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The Journal of Laboratory and Clinical Medicine

VOL. II. ST. LOUIS, JULY, 1917 No. 10.

ORIGINAL ARTICLES

THE BACTERIOLOGY OF POLIOMYELITIS

BY HORACE GREELEY, M.D., BROOKLYN, N. Y.

LABORATORY CULTURE MEDIA AND METHODS.

IN all bacteriological investigations it is essential to have standard methods which have been thoroughly tried and which are sufficiently numerous and different to enable one to adduce and detect variations in the behavior of any organisms which we may encounter. Although within the forty years which, approximately, cover the history of bacteriological discovery many methods for the laboratory cultivation of bacteria have been devised, yet there are but few which represent such really distinctive conditions as serve to distinguish one organism from another or which serve to cultivate an organism while others fail. The failure of the usual laboratory procedures to grow particular recognized parasites has been accounted for by the statement that living tissue or the conditions of the animal body were essential for its well being. However, the introduction of the fresh tissue media, as in the cultivation of the spirocheta pallida, removed the difficulties in the case of several organisms, and led bacteriology a step further ahead. In the employment of fresh tissue, such as the kidney of the rabbit, so long as we are dealing with an organism which is in no danger of being confused with contaminants one is entirely safe, especially when but one culture medium and method is followed and experiments are carefully controlled. But should we be searching for an unrecognized or a but partially known parasite, and in the course of our study transfer cultures from one form of medium to another, as from anaerobic serum plus fresh tissue, to aerobic solidified serum, we will meet unexpected difficulties since organisms introduced in the piece of fresh tissue that, perhaps, represent the flotsam-and-jetsam that fall into an animal's blood stream, frequently develop in one or the other of our

culture media and cause much trouble. Thus I have commonly found a contaminant of rabbits' kidneys when they are crushed and smeared over Loeffler's blood serum and the medium incubated aerobically—especially when treated as in the following.

A NEW METHOD.—These observations caused me several years ago to attempt to devise a substitute for the fresh tissue, and in so doing it was reasoned that since one known difference between living blood plasma and blood serum was the separation of the fibrin, and that since in this process a precipitation in which a calcium compound was involved was understood to take place it might be well to try the usefulness of blood serum (sterilized by the fractional method) plus a soluble calcium salt. Reasoning that as in the animal economy the cir-

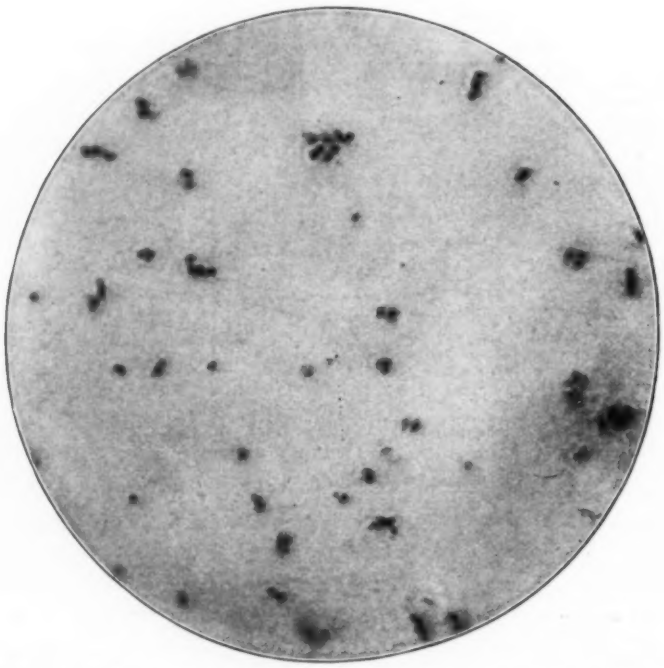

Fig. 1.—Smear from culture made from cord of Case I. Grown 4 days, anaerobically, in 25 per cent hydrocele fluid mixed with 75 per cent bouillon-limewater (equal parts of each). Methylene blue stain. Magnification, 1500. Photograph reduced one-fourth.

culation removed all acids, including carbon dioxide, it was thought that calcium oxide was the best available lime salt, since it was sufficiently soluble to supply a calcium base and would also fix any acids developing, especially the carbon dioxide. Various experiments with this medium (blood serum and limewater) developed the fact that a diluent of bouillon, in various proportions, greatly enhanced its suitability for various bacteria. Modifying this combination to the cultivation of bacteria upon a solid surface (as Loeffler's blood serum) it was found that to the desirable properties of both media could be added that of a continuously wet surface, by depositing a few drops of the serum-bouillon-limewater at the bottom of the slanted Loeffler serum tube, just prior to its inoculation, and tilting the tube once or twice a day, while in use, to cause the fluid

to flow over the inoculated surface, a procedure which also might be thought to act similarly to the blood current in mechanically washing away bacterial waste products. This method was employed extensively in the experiments to be detailed.

SOURCE OF CULTURE.—Cord and brain specimens from autopsies on eight fatal cases of the recent New York City epidemic were used. In five instances the specimens were from one to six weeks old and had been preserved in 50 per cent glycerine and kept on ice. In three instances specimens of brain and cord tissue direct from autopsies were employed. Specimens from one of the cases showed contaminating organisms and, as a precautionary measure, the cultures were discarded.

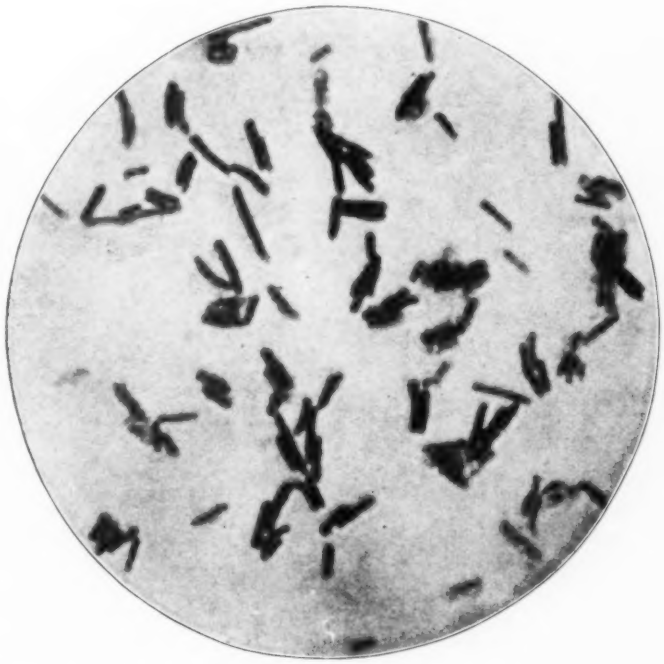

Fig. 2.—Smear from culture made from brain of Case IV. Sixth generation, grown two days, aerobically, on Loeffler's blood serum, washed with bouillon-limewater (lactose 4 per cent). Methylene blue stain. Magnification, 1500. Photograph reduced one-fourth.

Later, for the purposes of comparison, a culture isolated by a western bacteriologist was used.

METHODS OF CULTIVATION.—Series of cultures were made from all specimens: (A) In the Flexner-Noguchi fresh tissue medium; (B) in human serum (hydrocele fluid) 25 parts, diluted with 75 parts of 50 per cent limewater in nutrient bouillon,* and (C) on Loeffler serum tubes wet, as described, with the hydrocele-bouillon-limewater. (D) Control cultures were made on plain nutrient agar, and on plain Loeffler's serum (solidified).

*Lactose, 2 per cent, was also added, but later proved nonessential. The proportion of hydrocele fluid was also increased in some cultures.

Incubation was made at 37.5° C., anaerobically (media covered with liquid paraffine) in (A) and aerobically in (B), (C) and (D).

CHARACTER OF CULTURES OBTAINED.—Cultures from both brains and cords of the seven cases considered (made by dropping small pieces of each in fluid cultures, and by smearing pieces over the surfaces of the solid media) and the western culture—in all, fifteen cultures—gave results as follows:

Flexner-Noguchi medium (A): In 100% hydrocele fluid, plus a piece of fresh kidney, a slight cloudiness of the media developed by the third day, and smears made at this time showed a pleomorphic organism identical in appearance with that in the microphotographs illustrating Noguchi's article in the *Journal of Experimental Medicine*, October 1, 1913. Appearances were similar in smears

Fig. 3.—Smear from second generation of culture shown in Fig. 2. Planted on Loeffler's blood serum which, at the end of two days—no growth having appeared—was submerged in bouillon-limewater (dextrose 1 per cent). Smear made one day later. Gram's stain. Magnification, 1500. Photograph reduced one-fourth.

from all of the fifteen cultures. Limed Serum Bouillon (B): Cultures made in this medium grew much better than in the foregoing and showed a distinct cloudiness on the second day. Smears gave an organism similar to that before mentioned. Loeffler Washed with Limed Serum Bouillon (C): By the end of 48 hours, small, pinhead sized colorless colonies appeared on the surface of the medium. Smears made at this time showed an organism very similar to that produced by the other methods. When, however, the washing and incubation was continued another 48 hours, slight digestion (peptonization) of the medium began, and smears made at this time showed a sporulating bacillus, that is one that stained bipolarly, and of which the polar bodies were to be seen, some still within the bacilli, some in the act of escaping from the poles of the bacilli, and some en-

tirely free from the parent form.* Occasionally clubbed-shaped bacilli, similar in appearance to sporulating tetanus bacilli were encountered (Fig. 3). Later than the fourth day all bacilli had involuted, showing as hollow ovoids, such as would usually be denominated spores. Yet since the polar bodies, which are evidently the germinating elements, tend to escape at this time, this name in its accepted meaning is hardly applicable. Nutrient Agar (d): At the end of a week no growth had appeared. (The same was true of cultures made upon plain Loeffler blood serum).

TRANSPLANTS.—While the first generation of all cultures, either in the Flexner-Noguchi medium, in the limed-bouillon serum, or on the Loeffler, washed with the same, gave organisms the only difference between which appeared to be a variation in size, and which were Gram-positive, transplants seemed to indicate actual biological variations. Six cultures (numbered 1 to 6) from as many sources were conducted through a number of generations, on various media, with results as follows:

Culture 1.—Replanted from washed Loeffler to plain solidified Loeffler gave, within 24 hours, a creamy growth which by the end of the third day became slightly wrinkled and showed slight liquefaction of the medium. The organism appeared as small Gram-negative bacilli, of which some showed one or two Gram-positive poles. By the third day the bacilli with polar bodies "sporulated,"—assumed an oval nonstaining form, from which the polar bodies were often seen escaping. By replants, made at the end of 24 hours' growth, this culture was continued for eleven generations of identical qualities. The eleventh generation was then transplanted to nutrient agar, and within 24 hours developed as a white scum containing organisms which varied from both large Gram-negative and Gram-positive bacilli to diplococci of similar staining variations.

A replant of the last mentioned culture to bouillon-hydrocele-limewater gave a heavy growth of similar organisms. A replant from the fluid culture to Loeffler's solidified serum gave a distinctly wrinkled scum of mostly Gram-positive bacilli which proceeded to "sporulation" and marked liquefaction of the medium by the third day.

Culture 2.—Replanted as with Culture 1, gave at the end of 24 hours a wrinkled white scum of mostly Gram-positive bacilli, which "sporulated" and liquefied the medium by the third day. The same results were continuously produced for eight generations. Replant from the sixth generation into bouillon-hydrocele-limewater gave, by the end of five days, a faintly cloudy medium containing a good many minute Gram-positive diplococci and streptococci.

Culture 3.—Replanted, as above, for eleven generations, gave at the end of 24 hours a creamy, but partly wrinkled, scum containing large Gram-negative bacilli, among which could be found a good many Gram-positive ones. Liquefaction of medium varied from none to marked, by the third day. A replant of the eleventh generation into bouillon-hydrocele-limewater gave, by the fifth day, a few Gram-positive diplococci.

Culture 4.—Replanted as above for eight generations gave, at the end of 24

*Since writing this there has appeared (Jour. Bacteriol., March, 1917) a very interesting article by Mellon, describing the metamorphosis of a diphtheroid bacillus into streptococcus-like formations.

hours, a creamy growth of large bacilli most of which were entirely Gram-negative. A few, however, were always Gram-positive or had Gram-positive poles. In most cases there was slight liquefaction of the medium by the second day. The eighth generation, replanted into the fluid medium last mentioned, gave, by the fifth day, a few Gram-negative diplococci. A replant of this culture left at room temperature for several days developed two lemon yellow colonies of large Gram-negative diplococci—indicating a very interesting and perhaps most important biological variation.

Culture 5.—Replanted as with the foregoing, gave a slight creamy growth, which, for ten generations, failed to show the slightest liquefaction of the medium, and which consisted almost entirely of large Gram-negative bacilli (an occasional Gram-positive pole could usually be found). The tenth generation, replanted into the fluid medium previously mentioned, gave a growth containing organisms

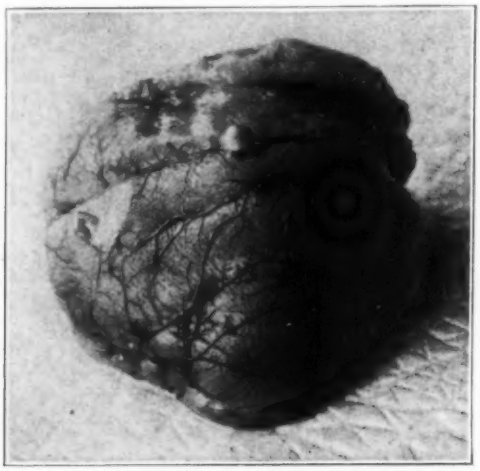

Fig. 4.—Cerebrum of young guinea pig which contracted a poliomyelitis bacillus infection from contact with another guinea pig intraperitoneally inoculated with the organisms of Culture 4 taken from the throat of an experimenter accidentally infected with this culture. One platinum loop of throat mucus in 0.5 c.c. saline was used.

varying from Gram-negative bacilli to Gram-positive diplococci. By replanting the eighth generation into bouillon and then returning it to Loeffler, a creamy and slightly wrinkled growth was obtained, which produced a slight liquefaction by the second day.

Culture 6.—Replanted from "blood agar" (on which it had been grown as Gram-positive streptococci) to Loeffler, washed as detailed, gave, by the fourth day, many small white colonies containing coccoid bacilli which were intermediate in the way in which they were affected by Gram—they were neither distinctly positive nor negative. A replant to the same medium gave, by the fourth day, a growth which began to show liquefaction and in which the organisms of the softening areas had developed to the "sporulating" large Gram-positive bacilli. From this last culture the same form (large Gram-positive sporulating bacillus) was propagated on plain Loeffler for ten generations and then transferred to serum (plural exudate) to which a small amount of calcium oxide had been added.

Cultivated in this for six generations (five days a generation) a growth consisting almost entirely of fine Gram-positive diplococci was developed.

General Considerations of Variations Observed.—*Form.*—It is seen from the above that growth in serum-containing fluid media tends to cause the organism to assume the coccoid form, even after extensive cultivation as a distinct bacillus on other media.

Development to the sporulating, Loeffler liquefying, bacillus is seen to be easily secured by growth upon this medium washed with limed-hydrocele-bouillon mixture.

It should be emphasized that for the complete transformation of the coccus form into the bacillus form of the organism, or vice versa, sometimes many generations are necessary. The sporulating bipolar bacillus evidently is the fully developed organism, and the tendency of all cultures is to develop into this. Therefore, it is easy to derive the bacillus from the coccus form, but more difficult to change a culture in the bacillus form into the coccus form. Thus a replant of the bacillus form in serum (fluid) often grows with difficulty, and the first generation or so show many bacilli, and forms intermediate between bacilli and cocci. Also, the elimination of all bacillus forms from such a culture often requires a good many transplantations. Further, individual strains (cultures from different sources) of the organism vary considerably in their amenability to these transformations.

Gram.—Gram-positive staining properties were developed in limed serum mixtures, and were also manifested whenever the complete development of the organism took place, i. e., when polar bodies were formed. In transplants from a medium conducing to the development of Gram-positiveness to one tending to make the organism Gram-negative, or vice versa, it is to be noted that a few organisms, retaining the parent's characteristic, usually appeared in at least the first transplant. But when the new conditions were continued in further generations such "reversions" tended to disappear.

Ferment.—Liquefaction of the Loeffler seemed to depend upon whether the organisms in a given culture reached the sporulating stage in large numbers or not; so it seems that sporulation frees the ferments that cause this phenomenon. Note that whenever the Gram-negative, nonsporulating form persisted no liquefaction appeared. Difficulty was experienced, as has been noted, in causing Culture 5 to liquefy Loeffler, and it was only by replanting, on Loeffler, organisms from a pellicle which had formed on a bouillon culture that this was finally effected.

Gas Production was noted in the case of Culture 1 only. When first isolated, the organism of this culture failed to produce gas on several trials. Later a small amount of gas was produced in bouillon containing 1% dextrose. No gas was produced by the organisms of the other cultures tested, although it is believed that all could be got to effect its production, by more extended effort, just as was the case with Culture 1.

Indol.—After a growth in 1% peptone water for six days, the nitrosoindol test (Salkowski) was applied with the following results:

Culture 1 Faint pink ring.
Culture 2 None.
Culture 3 Faint pink ring.
Culture 4 Distinct pink ring.
Culture 5 None.
Culture 6 None.

Indol production (detectable by this test) is therefore, probably, an unstable characteristic of the organism and, I believe, could be obtained with any culture.

Reaction of Cultures.—Replants of six cultures were made in two sets of tubes of bouillon colored with litmus, one set slightly acid and the other faintly alkaline. Growth was obtained in both sets and while no change in color in the acid set was observed the blue color of the alkaline set had changed, by the end of a week, to a greenish. We may, therefore, conclude that the organism produces acid in bouillon cultures.

Motility.—Original plants in fluid media of high serum percentage show no motility, unless a tumbling motion of individual "coccoids" may be denominated such. Replants, however, in fluid media not containing serum, show a motility which varies with the culture—sometimes sluggish or entirely absent, but commonly very active. A replant of a motile culture in serum media commonly gives a non-motile organism.

Smears from motile cultures showed that the organism has a single short terminal flagellum (Van Ermengem's stain).

Filterability.—Cultures (from eight sources), in limed-hydrocele-bouillon (2 days' growth) and three day liquefying cultures on Loeffler were passed through Berkefeld filter No. V. Plants made from the sixteen filtrates gave profuse growths similar to the original cultures.

Temperature of Growth.—Replants of cultures from eight sources (including western) were planted on plain Loeffler and incubated at 75° F. When it was found that good growth was obtained, a similar set was incubated for 48 hours at 70° F. ("summer heat"). Six of these cultures showed a profuse development, and two only a faint growth. First generation replants from the latter gave a profuse growth under the same conditions within a second 48 hours.

Cultivation in Milk and Resistance to Pasteurization.—Cultures of the eight "strains" mentioned were sown in two sets of tubes containing sterilized milk of the market variety (24 hours old, slightly acid to litmus) and one set incubated at 98° and the other at 70° F. for 48 hours. At the end of this period all cultures were swarming with minute coccoid bodies, and yet no apparent change had taken place in the milk, with the exception of Culture 1, grown at 98°, which had coagulated. Both sets of cultures were heated in a water bath for 30 minutes at 142° to 145° F. and replants from all then made. Good growths resulted in all instances. This experiment was repeated again, only allowing 24 hours for the development of the organisms in the milk. At the end of this period organisms were plentiful in all the cultures, but much fewer in those grown at 70° than in the corresponding tubes incubated twice the time (48 hours). No coagulation took place with Culture 1. All cultures survived the pasteurization process (30 minutes, 142° to 145° F.) and gave profuse growths on replants thereafter.

ANIMAL TESTS.—

Rabbits.—Among fourteen rabbits of a series (each injected in the ear vein with from ¼ to 1 c.c. of a fluid poliomyelitis culture—bacillus form) two developed a flaccid paralysis of one hind leg, noticeable on the third day, and one a partial paralysis, showing as weakness of hind legs. No other symptoms, except general weakness, were noticeable. The last mentioned died on the fifth day, and two others were killed, and autopsies made on the three. Meninges of brain and cord, and portions of the gray matter beneath, of the three were markedly congested, and microscopical examination showed areas of infiltration around blood vessels.

One rabbit died without manifest symptoms, on the second day following inoculation, and autopsy showed the same meningeal and gray matter engorgement.

Ten rabbits showed no definite symptoms, but three of them, killed on the fourth day following injection, showed considerable congestion of brain and cord.

Cats.—Similar inoculations made into the saphenous veins of young cats gave results as follows:

Two died on the fourth, and one on the sixth day, after having shown extreme prostration and having refused all food. During the four days of illness all manifested a nasal discharge, and sneezed very frequently.

After showing similar symptoms, eight cats recovered within periods ranging from two days to two weeks.

One cat, on the second day, developed marked paralysis of the back muscles and a weakness of one hind leg. Two others showed a transient paralysis manifested by distinct "weakness" of hind legs. The last three animals also showed a nasal discharge, with accompanying sneezing.

All of the cats were given from 0.6 to 2 c.c. of a fluid culture.

Autopsies on the three cats that died, and on five that were killed within two weeks following injections, showed similar lesions to those found in the case of the rabbits, in one, however, small cerebral hemorrhages had taken place.

Dogs.—Swabs soaked with a fluid culture were rubbed over the nasal mucosa of two young dogs with the result that from the second day for about two weeks one manifested a severe and the other a mild catarrh. The first showed considerable discharge but the latter only frequent sneezing.

Another (a young fox terrier) inoculated in the ear vein with 1 c.c. of a fluid culture was made very ill for about a week with symptoms of prostration, fever, and frequent sneezing. At the end of this time, as he apparently was recovering, a second dose of double the quantity was given in the same manner. The next day he was apparently quite sick but showed no catarrhal symptoms. On the second day he was very weak in the hind legs and, towards evening, I noticed that he carried his right hind leg, which was evidently partially paralyzed. On the third day his left fore leg was likewise affected and, while he could use it in standing, it was very weak. This dog's bladder was also involved in the paralysis, since urine dribbled when he moved, or when his abdomen was struck.

Another young dog, inoculated with 3 c.c. of the same culture, died on the fourth day, after great prostration and some catarrhal manifestations.

One adult dog, inoculated with 1 c.c. of the culture, showed no symptoms beyond apparent fever and anorexia lasting about 24 hours.

Two puppies, four weeks old, each intravenously inoculated with 1 c.c. of the culture developed within 24 hours extreme prostration and marked catarrh which within three days showed as a marked nasal discharge. Both dogs died on the fifth day. The three dogs that died and the other four, which were chloroformed a week after receiving their dose of the culture, were autopsied.

The two dogs, of which the nasal mucosa was swabbed with a culture, showed no lesions beyond a congestion of the mucous membrane mentioned.

The paralyzed dog showed marked congestion and infiltration of both brain and spinal cord, together with a number of small hemorrhages into the gray matter of each.

The unaffected adult dog showed a congestion of the meningeal vessels, principally those of the brain.

The lesions in the three dogs that died were more marked: All had extreme congestion of the meningeal vessels of both cord and brain, and a marked infiltration of the adjacent gray matter. Small hemorrhages into the gray matter and from the meningeal vessels were common in the three dogs.

Lesions Outside Nervous System.—Autopsies of all the animals—rabbits, cats, guinea pigs, and dogs—that died as a result of the inoculations disclosed general hemorrhagic tendencies especially marked in the subcutaneous vessels. One such cat, two rabbits, one guinea pig and a dog, of the same category also manifested considerable congestion of the kidneys, and in the case of the last mentioned cat both spleen and liver were markedly swollen. The nasal mucosa of nearly all of the animals was congested in varying degree. One rabbit also showed a severe general congestion of both lungs.

From the brains of all of the animals described, that died or were killed, the organism was recovered in pure culture.

The similarity of the symptoms of experimental poliomyelitis in animals, as evidenced in the preceding experiments, and those of others, to the disease known as distemper is most interesting.

No inoculations (except of the one rabbit described) were made directly into the central nervous system, since it was felt that paralysis might follow such operations even in the case of organisms which could never naturally affect it.

Relationship of Poliomyelitis and Distemper.—Among dogs suffering from distemper paralysis develops in a small percentage of the animals.* For in-

*In connection with the frequency and form of nerve center involvement in distemper of dogs, the following quotations are of interest:

"In a few cases the disease leaves after it a permanent paresis of the hind-quarters and a vesicorectal paralysis. We have several times noticed paralysis of the tongue." (Friedberger and Frohner: Path. and Ther. of the Domestic Animals, ii, 35.)

The same authority says that "cerebral edema" is usual, and also "slight edema of lumbar region" of the cord. In "acute paralysis," accompanying distemper in dogs, an exudate is found around the blood vessels of the nerve center and a degeneration of the latter. In "chronic paralysis," "circumscribed interstitial myelitis, with partial atrophy of the nerve substance," is the rule (Ibid., 354).

"Paralysis may follow the convulsions (in distemper) or it may come on simultaneously with them. It seldom occurs at the beginning of the disease. It may be confined to certain groups of muscles, as those of a limb, the whole of the hind-quarters, or even involve the entire body in the form of paresis, especially of the motor nerves, combined with excessive muscular weakness.

"Usually the brain is the seat of edema. In some cases the brain substance, especially the walls of

stance, during six months, ending Nov. 30, 1916, the pay clinic for dogs of the A.S.P.C.A. (in New York City) treated 3,055 dogs, and 506—16.5 per cent—of these are recorded in the clinic register as suffering from distemper. Among these distemper cases only about 5 per cent showed paralytic symptoms or signs of nerve center involvement.

It is well known that cats suffer from distemper due to infection by the same organism that causes the disease of dogs, but a cat so affected only occasionally shows paralysis.†

The following, partly inadvertent, experiment is interpreted as strongly indicating the identity of the two organisms (poliomyelitis and distemper). In injecting a cat (intravenously) with a culture of the organism, and wishing to give a second syringeful of the material, I detached the needle, leaving it in the vein, and refilled the syringe, then returned it to its connection with the needle. Resistance was, however, met to the flow through the needle (owing probably to a blood clot) and when I added extra pressure to the piston some of the culture squirted out around the needle-syringe joint, a drop reaching one of my eyes. It was carefully washed out with a solution of a silver salt and I thought no more about it. About 72 hours later I felt a slight soreness of the throat and some signs of digestive disturbance, including a slight headache. Temperature was not taken, but if it was elevated at all, it must have been very slightly. I went ahead with my usual routine, never suspecting anything but one of the every day indispositions with which everyone is occasionally troubled, although I afterwards realized that I had felt very unusually nervous, all day. After I got to bed I could not, as I, as a rule, invariably do, get to sleep at once, but had to sit up repeatedly owing to an unexplainable feeling that I could not breathe. There was not the slightest interference with control of any respiratory act nor of any muscle. Through the night I slept very little, owing to a repetition of this uneasy sensation. The next day I felt fairly well, though slightly weak, which continued to be the case for several days.

The following morning I began to suspect that the cause of the sensation might be a poliomyelitis-organism pharyngitis, and determined to investigate. The post-pharyngeal mucous glands appeared markedly swollen, and scrapings disclosed a great many spear-head shaped "streptococci-like" organisms, which subsequently gave developments on cultivation identical with those of the culture I had used on the cat.

The same day, four platinum-wire loopfuls of mucus from my pharynx were mixed in 1½ c.c. of saline solution, and 1 c.c. injected, intracerebrally into a rabbit, and ½ c.c. intraperitoneally into a young guinea pig. The rabbit developed paralytic symptoms within 24 hours, affecting principally the adducter muscles of his legs, but as he fell about considerably I thought that his sense of equilibrium was affected (Fig. 5). This rabbit appeared to be recovering for some days, but finally died, and the autopsy showed marked engorgement of the

the vessels, is infiltrated with leucocytes. Changes in the spinal cord, which are not well marked, consist chiefly of anemia and slight edema, especially in the lumbar region." In acute paralysis, there are changes in the walls of vessels, with an exudate along the vessels and in the interstitial tissue of the gray matter of the spinal cord. In chronic distemper there is a localized interstitial myelitis with partial atrophy of the cord: (Moore: The Pathology and Differential Diagnosis of Diseases of Animals, 343).

†Ibid.

brain and cord, and, microscopically, much round cell infiltration and a considerable number of organisms that upon cultivation proved to be identical with those of the original culture.

The guinea pig died on the fourth day, and the postmortem showed congestion of the meningeal vessels of the cord. Those of the brain were extremely congested, and in many places had given rise to small hemorrhages. Everywhere in the substance of the brain the same engorgement of the blood vessels was apparent, and many extravasations of blood were found. Round cell infiltration of the adjoining brain matter was distinct. Cultures, from the brain and cord, gave the organism of the culture originally used.

The above mentioned guinea pig had been kept in the same cage with another of the same age, an adult guinea pig and a young rabbit. Five days after the death of the first guinea pig I found the companion guinea pigs dead, and

Fig. 5.—Rabbit intracerebrally inoculated with 1 c.c of saline containing two platinum loopfuls of mucus from the throat of the experimenter accidentally infected with Culture 4. Photograph taken three days before death.

the rabbit sick. Autopsies of the two guinea pigs disclosed extreme congestion of the vessels of the brains and cords, with small hemorrhagic extravasations here and there, upon and in the brain tissue, and accompanying round cell infiltration.

An illustration herewith shows the congestion of the meningeal vessels of the second young guinea pig (the contact case).

The contact rabbit died 24 hours later and a similar involvement of the nervous system, without other apparent lesion, was found on autopsy. The brains and cords of these three animals gave the organism of the culture originally used on the cat.

Feeding Experiments.—The carcasses of the two infected-by-contact guinea pigs were fed to two cats, one of which developed the symptoms of distemper (catarrah and prostration) with the apparently identical organism in the discharge. The attack took four days to develop and lasted about a week.

Two cats fed on 2 c.c., and 3 c.c., respectively, of cultures (grown in milk) developed a copious diarrhea which lasted seven and ten days, respectively.

The Organism from Naturally Acquired Distemper in Animals.—Something should be said here in regard to the organism causing distemper in animals, and its characteristics:

I find it stated, generally, in textbooks and the other literature, that all (or most) of the domestic animals suffer from infectious processes due to organisms which are at least allied to the bacillus causing the distemper of dogs and cats. Characteristics common to all of the organisms so operative are described as follows:*

"Characteristics common to the pasteurella group.—Organisms of the pasteurella group are nonmotile coccobacilli, Gram-negative, very pleomorphic, and staining more deeply at the ends than in the center. They do not form spores, do not liquefy gelatin nor coagulate milk, they give no visible growth on potato, are primarily aerobic, but can be grown anaerobically. They give rise in culture to a peculiar and characteristic odor.

"According to Lignieres, these organisms do not produce indol in culture, but old cultures of the bacillus of fowl cholera (the avian pasteurella) certainly contain indol."

Besson, the author of the textbook quoted, describes the organisms of this group under the general term "Pasteurellas" and, in regard to the group as a whole, writes:†

"As Nocard held, the organisms isolated from different animal species must be regarded as varieties of the same bacillus, and the conclusion arrived at is in short this: that there is one Pasteurella, which can pass from one animal species to another, and which by adaptation in one species can produce a disease peculiar to that species."

Last fall I obtained cultures from three dogs suffering from canine distemper, in order to compare the organism with that from poliomyelitis, with the following results:

Mucus from the nares and nasal discharges of all three dogs showed great numbers of small bipolar bacilli which varied considerably in size, and in their response to the Gram stain—in the same smear some appearing Gram-positive, some Gram-negative, and some intermediate (not positively either positive or negative). Cultivation of these organisms, by the methods detailed in connection with the poliomyelitis cultures, gave growths of an organism which corresponded in all particulars (not detailed as space would hardly permit) with the poliomyelitis bacilli. There were slight differences, to be sure, but only similar ones to those between poliomyelitis cultures of different source.

However, the characteristics of the distemper bacilli isolated did not correspond in some important particulars with those given for the class in the quotation from Besson: they could be grown to show motility‡ and also involution forms resembling spores. In these particulars they varied just as did the poliomyelitis bacilli; in accordance with the method of cultivation.

*English Edition of Besson's "Practical Bacteriology, Microbiology, and Serum Therapy," p. 447.
†Ibid., 446.
‡McGowan (Jour. Path. and Bacteriol., xv, 372) stated that the bacillus of dog distemper was "slightly motile."

The culture denominated Distemper I, mentioned in this article, was obtained from a hound under the care of Dr. Little, Veterinarian in charge of the A.S.P.C.A. clinic, previously mentioned.

Agglutination tests of this bacillus, against specific antipoliomyelitis sera, and against the blood of poliomyelitis convalescents are given in the accompanying tables. Results vary much as with poliomyelitis cultures.

TABLE I.

SUMMARY OF AGGLUTINATION TESTS.*

BLOOD SPECIMENS.

In dilutions of 1:40—

11 blood specimens completely agglutinated one or more of the six cultures.
In this dilution:

7	specimens	completely	agglutinated	1 culture each.
3	"	"	"	2 cultures "
1	"	"	"	3 " "

In dilutions of 1:20—

26 blood specimens completely agglutinated one or more of the six cultures.
In this dilution:

14	specimens	completely	agglutinated	1 culture each.
8	"	"	"	2 cultures "
2	"	"	"	3 " "
1	"	"	"	4 " "
1	"	"	"	5 " "

In dilutions of 1:10—

37 blood specimens completely agglutinated one or more of the six cultures.
In this dilution:

9	specimens	completely	agglutinated	1 culture each.
12	"	"	"	2 cultures "
6	"	"	"	3 " "
5	"	"	"	4 " "
3	"	"	"	5 " "
2	"	"	"	6 " "

CULTURES.

Number		Dilution 1:10	1:20	1:40
1	Times completely agglutinated	11	4	1
2	" " "	24	12	4
3	" " "	10	4	1
4	" " "	20	9	1
5	" " "	22	14	8
6	" " "	11	2	1

*Thirteen (13) specimens failed to completely agglutinate any of the cultures. It is noteworthy that all the acute cases (6) were among this number.

Serum tested was from three cats, injected each three times with increasing doses of cultures. Serum A was made with Culture 1; Serum B, with Culture 3; and Serum C, with Culture 4 (Table II).

SEROLOGY.—Agglutination Tests.—Table I contains a summary of 1500 agglutination tests made with the blood of fifty children, stricken with poliomyelitis in the recent epidemic in New York City. Thirty-six of the children were in the Seaside Hospital, Brooklyn, nine in the Riverside Hospital (for acute cases), one in the Long Island College Hospital and four under the care of various Brooklyn physicians.

In all, except one case, dried blood was used in making the required dilutions, which were standardized by color. The dilutions are recorded in parts of blood

(not serum) so that 1 to 10 agglutination represents 1 part of blood in 10 parts of saline and culture.

In glancing over the table it will be seen that no blood completely agglutinated in dilutions greater than 1 to 40, and, we find that in this dilution but 11 of the 50 specimens were effective. In dilutions of 1 to 20, 26 specimens completely agglutinated one or more cultures, and in 1 to 10, 37, while 13 failed to completely agglutinate any culture.

In Table II are recorded agglutination tests made with sera from cats which

TABLE II.

ANTIPOLIOMYELITIS SERUM AGGLUTINATION TESTS.

(Tests recorded after incubation for one hour at 98° F.)

Serum	A							B							C						
Culture	1	2	3	4	5	6	D	1	2	3	4	5	6	D	1	2	3	4	5	6	D
Dilution of serum																					
1:10	C	C	C	O	C	C	C	C	C	C	S	C	C	C	C	C	S	C	S	C	C
1:20	C	P	C		C	C	C	C	C	C	O	C	C	C	C	C	S	C	S	C	C
1:40	C	S	C		P	C	P	C	C	C		P	C	S	C	P	O	C	O	S	O
1:80	C	O	S		O	C	S	C	C	C		S	C	O	P	S		C		O	
1:160	C		O			P	O	C	P	C		O	P		S	O		C			
1:200	C					O		P	O	C			O		O			P			
1:320	C							O		P								S			
1:400	C									S								O			
1:500	C									O											
1:600	C																				
1:700	P																				
1:800	P																				
1:900	S																				
1:1000	S																				

Key: Cultures 1 to 6 are the same as those so numbered in Table I. Culture D is of distemper bacillus I. O, S, P, C denote: no, slight, partial, and complete agglutination, respectively.

TABLE III.

POLIOMYELITIS BLOOD AGGLUTINATION OF DISTEMPER BACILLUS I.

(Tests recorded after incubation for one hour at 98° F.)

Case No.	35	36	37	38	39	40	41	42	43	44	45
Dilution 1:10	O	P	C	C	P	P	O	P	C	O	P
1:20		S	C	C	S	S		S	P		O
1:40		O	P	P	O	O		O	S		
1:80			S	S					O		
1:160			O	O							

Key: O, S, P, C, denote: no, slight, partial, and complete agglutination, respectively.

had been immunized against poliomyelitis cultures to such a degree that (Serum I) ten times the ascertained usually fatal dose failed to affect. From this table we see that one culture was completely agglutinated in dilutions of 1 to 600, which shows that the poliomyelitis organism is quite susceptible to this process.

Table III (referred to elsewhere) shows the agglutination of a distemper bacillus by poliomyelitis blood.

In Table IV are recorded agglutination tests made with sera of adults and children who had never had poliomyelitis. The minimum strength in which any

of these bloods completely agglutinated any of the six cultures was 1 to 20, 4 out of 10 specimens agglutinating in this strength.

From these facts we can at least compare the strength of naturally acquired immunity in man and that which may be induced by vaccination, as measured by the agglutination test, a comparison which is seen to promise well in reference to the possible effectiveness of antipoliomyelitis sera, since serum A was at least 15 times as powerful as the "strongest" blood from a convalescent child.

TABLE IV.

NORMAL HUMAN BLOOD AGGLUTINATION.

(Tests recorded after one hour at 98° F.)

Number	1A	2A	3A	4A	5A	1C	2C	3C	4C	5C
Poliomyelitis										
Culture 1										
1:10	O	S	S	O	P	O	O	P	O	O
1:20		O	O		S			S		
1:40					O			O		
1:80										
Culture 2										
1:10	C	C	C	C	C	O	S	C	O	O
1:20	P	C	C	C	P		O	C		
1:40	S	P	P	P	S			P		
1:80	O	S	S	S	O			S		
Culture 3										
1:10	O	C	P	O	S	O	S	C	O	O
1:20		C	S		O		O	P		
1:40		P	O					S		
1:80		S						O		
Culture 4										
1:10	P	C	S	C	S	P	P	C	O	O
1:20	S	P	O	C	O	S	S	C		
1:40	O	S		P		O	O	P		
1:80		O		S				S		
Culture 5										
1:10	O	S	P	C	S	O	P	C	O	O
1:20		O	S	C	O		S	C		
1:40				P			O	P		
1:80				S				S		
Culture 6										
1:10	O	O	O	O	S	O	O	P	O	O
1:20					O			S		
1:40								O		
1:80										

Key: Same as for Table III. Specimens are numbered in two series—those from adults comprising the A series, those from children the C series. In the case of the adults, serum was used; in the case of the children, dried blood.

As only three inoculations of the animal were made in producing this serum, it may be surmised that a much more powerfully agglutinative serum might easily be developed.

In reference to the normal blood reactions, recorded in Table IV it should be mentioned that 2C and 3C are from two sisters, residents of Brooklyn, and exposed to the recent epidemic; and that 4C and 5C are from children in other communities not visited by the disease. Case 1C is from my own son, a boy of 16 years of age, and is particularly interesting in that Culture 4, the only one

agglutinated at all, is the same as that of which a drop is recorded as having accidently entered my eye.

The reactions given by the adult blood specimens seem to be about such as we might expect from known immunes, as adults so generally are. All completely agglutinated at least one of the six cultures in dilutions of 1 to 10.

Specific Agglutinability of Individual Cultures.—In the tests with convalescent blood there are so many "overlappings," as it were, in which two or more blood specimens agglutinate the same and also different cultures, that it would be difficult to separate the cases into groups in accordance with the cultures agglutinated. However, with the specific antipoliomyelitis sera tested (in Table II) we find a markedly specific agglutination, as with serum A and its antigen, Culture 1. Something of the same is seen in the case of the other two sera and the cultures used to produce them.

Note should particularly be made of the fact that while serum A would not agglutinate Culture 4, the serum made with this latter (4)—Serum C—strongly agglutinated the culture of Serum A (1). Also that Sera B and C, respectively, only slightly agglutinated (1:10) the culture used to produce the other.

These are interesting, but not easily explicable, facts which, however, strongly point to the probability that in producing a serum for the treatment of poliomyelitis, polyvalence will be necessary.

ACUTE CASE OF POLIOMYELITIS TREATED WITH SPECIFIC SERUM.

While visiting Riverside Hospital to get nine of the blood specimens recorded in the preceding, (Table I) the resident physician in charge, J. W. Crawford, asked me if I knew where he could obtain some serum from an immune person, as the physician of R. Z., a 16 year old boy specially wished to have it tried, as he feared the patient otherwise had no chance of recovery. I told him of the cat serum that I had prepared and, after the patient's physician had been consulted and had urged that it be tried, this was done.

The cat sera were first tested for any possible agglutinative and hemolytic action which they might have on the patient's corpuscles, and Dr. Crawford then gave him intravenously a mixture of Sera A, B, and C, about 35 c.c. in all.

The patient had been paraplegic and had suffered from bowel and bladder paralysis since his attack began, six days before. His temperature had been constantly about 103° F., and he was very restless and complained of great pain along his spine. He was coughing considerably and a lung complication was believed imminent.

No effect was noticeable from the serum until about 24 hours after its administration, when the patient's bowels and bladder emptied themselves for the first time since his illness began, six days before; and the pain in his spine was markedly relieved. Relief in these particulars continued, but the boy's lung complication grew worse, and he died, three days later, of pneumonia of the left lung. This case was one of the last of the epidemic, and no other opportunity has since presented for further trial of the sera.

SOME EPIDEMIOLOGICAL FACTS IN RELATION TO THE BACTERIOLOGY.

The almost exclusive prevalence of poliomyelitis in summer has been a subject of much interest, and the marked subsidence of epidemics at the commencement of the cooler fall temperatures has been the cause of much speculation. Therefore, the fact, demonstrated in the foregoing, that the organism multiplies readily at "summer heat" (70° F.) is interesting, and, I think, very enlightening as to the cause of summer epidemics. Especially important seems the fact that the poliomyelitis organism grows well at summer temperatures in market milk, and that pasteurization does not kill it.

The literature is full of evidence as to how markedly epidemics of poliomyelitis are affected by the outside temperature, and, as a recent example, it is interesting to note the mean temperature, and the number of cases of poliomyelitis reported, in New York City, during each of the warm months of 1916:

MONTH.	MEAN TEMPERATURE.	CASES.
May	59.3°	29
June	64.2°	756
July	73.8° (over summer heat)	3863
August	73.6° (over summer heat)	3306
September	66.0°	780
October	57.2°	193

During the course of the epidemic that visited Washington, D. C., in 1910, the temperature varied between 69.7° and 77.6° according to the report of the special commission of investigation.

Recently I have gone over most of the literature on the epidemiology of poliomyelitis, covering more than 50,000 cases, and have noted the evidence contained therein that few or no babies develop the malady while exclusively breast fed. However, definite statements concerning the manner in which the affected children have been fed are few, and to such evidence we have to add that of the rarity of the occurrence of the disease in babies under one year of age—who alone would be likely to be so fed—and its extreme prevalence (in at least 90 per cent of all cases) in children under ten.

I have some of the statements found in the literature, bearing on this question: New York City (1907)—"121 cases exclusively breast fed among 283 under 2 years." Massachusetts (1907)—"None of 7 cases under 1 year were exclusively breast fed." Westphalia (1909)—"Considerable number of children at the breast were affected." Massachusetts (1909)—"No case among exclusively breast fed." Iowa (1910)—"Two cases exclusively breast fed among 47 considered." Cincinnati (1911)—"Fifteen cases exclusively breast fed among 83 considered." Buffalo (1912)—"Twelve cases exclusively breast fed among 40 considered."

How the age incidence of the malady indicates that few or no exclusively breast fed infants are affected is illustrated by the figures of the recent epidemic in New York City:

Total cases	9,023
Under 1 year	11%
1 to 5 years	68%
5 to 10 years	16%
10 to 16 years	2%
Over 16 years	3%

Note that while 95% of all the cases were under ten years of age, only 11% were under one year!

The bacteriological relationship of poliomyelitis of man to distemper of the domestic animals is illustrated, epidemiologically, in Table V, which I have compiled from the literature:

TABLE V.

ACUTE PARALYTIC DISEASE AMONG DOMESTIC ANIMALS COINCIDENT WITH EPIDEMIC POLIOMYELITIS.

POLIOMYELITIS EPIDEMIC.	ANNOTATION.	AUTHORITY.
Vermont (1894)	"Horses, dogs and fowls affected with paralytic disease."	Caverley: Jour. A. M. A., 1896, xxvi, 1.
Sweden (1905)	"Paralysis among dogs and other animals."	Wickmann.*
Dubois, Pa. (1907)	"Paralysis among pigs and chickens."	Free.*
Wisconsin (1907)	"Paralysis among colts, sheep, cats, ducks, and many other animals."	Manning.*
Oceana Co., Michigan (1907)	"Paralytic disease of chickens."	Griffin: Jour. Mich. Med. Soc., Feb., 1908.
Rhenish Westphalia, Germany (1909)	"Great mortality among chickens."	Romer: On Epidem, Kinderlah, Berlin, 1911.
Massachusetts (1909)	"Paralytic disease prevalent among animals."	Lovett: Month. Bull. Mass. St. Bd. of H., June, 1910.
Minnesota (1909)	"Colts, paralysis among."	Hill.*
California (1910)	"Paralysis among colts, dogs, cats, and chickens."	Snow.*
Washington, D. C. (1910)	"Paralytic disease appeared among ducks and chickens just prior to the outbreak."	Special Committee of Investigation.
Iowa (1910)	"Paralysis among cats, hogs, and chickens."	Bierring.*
California (1910-11)	"Paralytic disease coincident among domestic animals."	Gundrum: Cal. State Jour. Med., May, 1913.
Sao Paulo, Brazil (1910-11)	"1000 horses and 4000 cattle died with 'symptoms' of rabies."	Carina.*
Cincinnati (1911)	"Paralytic disease coincident among domestic animals."	Frost: Hyg. Lab. Bull., No. 90.
Indiana (1911)	"18 paralyzed animals associated with 102 cases of poliomyelitis."	King.*
Ohio-Kentucky (1911)	"Paralysis among chickens."	Batte.*
Alaska (1913)	"Outbreak was preceded by a great epidemic of distemper among the dogs."	Pierson: Jour. A. M. A., Feb. 28, 1914.

*Quoted by Frauenthal and Manning in their book on poliomyelitis, "Infantile Paralysis."

CONCLUSIONS.

It is demonstrated that the organism isolated from the nerve centers of cases of poliomyelitis (including the "streptococcus" described by various observers) is a pleomorphic bacillus of the distemper group, which varies in characteristics much as the various, supposedly different, members of the group do from one another; that this poliomyelitis bacillus could cause paralysis in cats, dogs, rabbits, and guinea pigs, and that an accidental passage of a culture through man gave rise to abortive symptoms of the malady; that after this last named passage it could produce paralysis in a rabbit, and a contagious infection of guinea pigs,

with nerve center lesions; and, finally, that from the guinea pigs it could produce distemper in cats.

Further it is shown that the organism is saprophytic and grows well in milk at "summer heat;" and that it resists the pasteurization process, while contained therein. Also, that it forms "spores," and is a "filter passer."

It seems very probable that, while contact cases of poliomyelitis may occur, either by direct transmission of the germ from animal to man, or from man to man, the great mass of cases which comprise epidemics are caused by milk borne contagion, and, furthermore, we shall have to regard our cows as possible "carriers" of the infection. It is, of course, evident that infection could get into milk from other animals, as the cat and dog, or even from a human carrier (as was supposed to have occurred in a series of cases reported by John C. Dingman, of Spring Valley, N. Y., in the December number of the *New York State Journal of Medicine.*)

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NEWER CONCEPTIONS OF DEMENTIA PRÆCOX BASED ON UNRECOGNIZED WORK*

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JUST as our knowledge of any given subject comes to being out of many little nebulous masses, so we have gained a certain amount of insight into the nature of dementia præcox. And as the science of any subject owes its accurate development to the work of the laboratory, so our present knowledge of dementia præcox has been built up from the many little nebulous masses, which have developed in the laboratory but which have developed into a concrete whole; paradoxical as the idea may seem. And yet, this disease form which makes up nearly a quarter of all the cases admitted to hospitals for the insane and which accounts, more than any other single factor, for the necessity of building more of such institutions, has been neglected from the only side which can possibly give us hope of combating its spread, the laboratory side. Its treatment has been largely custodial, symptomatic, not to forget recent developments in industrial teaching and in social service work.

Laboratories deal with technical methods and for this reason a discussion of our present knowledge of dementia præcox or a presentation of newer conceptions of dementia præcox from the laboratory point of view must be more or less intimately linked with a discussion of the methods used in obtaining the knowledge.

The institution of exact methods begins with the investigation of the cause of death by means of the postmortem examination. The earliest investigation of a case of dementia præcox that I have been able to find, where the brain and organs were examined and the examination published, was in 1844 by Alquié (quoted by Cramer[1] in 1896). The chief finding of interest to us is that the gray matter of the brain was injected. This observation I take to be of the utmost importance, not only because it was a true observation, doubtless, but because it is a frequent finding even today, though not confined to dementia præcox, of course. The method of observation is also important and the one most generally used in medicine. It is called the gross method or the macroscopic examination. Using this method, much valuable information has been obtained concerning the nature of dementia præcox.

Jehn,[2] in 1877, speaking of acute delirium, and some of these cases certainly look like dementia præcox mentally, remarks on a high grade of vascularity found; as did Alquié. There is hyperemia, clouding of the pia, reddening of the cortex, increased cerebrospinal fluid, and edema of the brain. There are changes in the other organs and the hemoglobin comes out of the blood. L. Meyer (1857), speaking of "acute fatal hysteria" mentions extensive veñous hyperemia (Cramer[1]). Pauly[3] (1869) in a dissertation at Bonn, mentions edema resulting from hyperemia. Schüle[4] (1879) separates two types of acute delirium—one showing hyperemia of the pia, a few with serous edema, especially of the frontal

*From the Pathologic Department, Worcester State Hospital, Worcester, Mass.
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lobes, some with milky, diffuse or punctiform clouding and reddening of the cortical surface of the meninges—the other group showing nothing in the meninges, but a venous hyperemia in the brain and an increase in the cerebrospinal and ventricular fluid. Rezzonico[5] (1884) gives the history of a male of forty-seven years of age who died after eleven days of excitement. There were no external signs of disease or injury, but the cortex and white matter were remarkably hyperemic. Similar observations were made by Ball[6] (1885) and Holsti[7] (1884). Thickening of the meninges without exudate is frequently seen, as noted by Klippel and Lhermitte (quoted by Zingerle[8]), Obregia,[9] Schütz[10] (1909), Lukacs[11] (1908), Marchand,[12] Goldstein,[13] and Weber[14] (1899). So hyperemia of the brain, thickening and adhesions of the meninges, were the observations of the day in cases which we can recognize today as being those of dementia præcox and of the infections or intoxications and these findings were linked with the interests of the day such as intracranial circulation, pressure, and stasis. Such were also the findings of Kahlbaum[15] in his monumental work differentiating katatonia, or tension insanity, as he called it.

The gross method was not exhausted with these observations but turned in new directions after many years. Examination of the convolutions came next with the claim that there was atrophy (Klippel and Lhermitte,[16] 1907), that there was decrease in size of the white matter and of the cortex (Obregia, 1906—Zimmermann,[17] 1907), that there was hemiatrophy and lobar atrophy of the cerebellum (French writers and later Morse and Taft[18]), that there was convolutional asymmetry (Mondio, quoted by Omorokow[19]).

Another form which the gross method took was the investigation of the relation existing between brain weight and cranial capacity. This was first made practicable by Reichardt[20] (1907-1911) who showed that there was little difference between the weight of the brain and the capacity of the cranium in certain cases of katatonia, dying suddenly, with or without convulsions. The same was true in some cases of epilepsy, the difference being 0%. Cases described by Nonne[21] as "pseudotumor cerebri" (1904) are of the same sort, and their histology has been described in detail by Rosental[22] (1911). These are cases which give evidence of tumor clinically, but prove the diagnosis to be wrong by cure or autopsy. Such a case was published by Dreyfus[23] (1907) from the Basle Psychiatric Clinic. The patient was a male dementia præcox of twenty-nine at onset, who died suddenly at 32 years of age. The brain was stained with several stains, in sections taken from eight different areas, and no changes were found but the cord was large for the spinal canal and the brain was 140 grams too heavy for the cranial capacity. Death was due to acute brain swelling.

The interval between these two great periods of research with the gross methods was taken up with the study of the minute details of brain pathology by means of the microscope and the newly discovered color chemistry. Most of the work on dementia præcox, as in other branches of pathology, has been done with the methods of finer histology, neglecting the more logical ones of photographing the gross changes observed so that they might be preserved for comparison in large numbers of cases from all parts of the world; neglecting the fact that study of the frontal section in series might yield something and this to be photographed; neglecting the fact that the whole brain microtome can give

valuable information in the psychoses; and going directly to the finer histology with the attempt to get the section ever thinner.

The results obtained over the years have been very much at variance and often appeared to be extremely contradictory, but the time has come when a certain uniformity can be put upon them and they can be understood.

To unify the large amount of material which has accumulated and at the same time to show that the changes found are very much alike, I have selected cases from the following groups and have arranged the results under the dementia præcox group, the confusional and delirious group, a single case of "pseudotumor," and the general work on the nervous elements in the psychoses.

In 1896 the findings in the acute case of the paranoia group were given by Cramer.[1] A male of twenty-four, duration seven days, had shown albumin and fatty casts. Temperature was 40.5° C., pulse 132, respiration 48. Autopsy was performed 10 hours postmortem. No leucocytes were found in the tissues. There was hemorrhage about the small vessels of the brain and thinning of the interradiary and tangential fibers in places. The writer concludes that a case not manic or melancholic but paranoiac or possibly confusional can show severe changes of a noninfectious character. This is the type of case we meet repeatedly in the literature, until we come to agree with Goldstein[24] (1910), that there are few uncomplicated cases in the literature; and we must finally agree that there can be no uncomplicated cases, if our methods of diagnosis and of pathological examination are adequate. Certain it is that the number of supposed uncomplicated cases has become remarkably few with rapid advances in accurate diagnosis and accurate protocol taking.

In 1906 Klippel and Lhermitte[25] described changes in the spinal cord of cases of dementia præcox. One case was that of a male of twenty-nine in which the cord showed changes in the posterior columns exactly like those seen in tabes. Another case, age thirty-five, gave changes in the lateral columns, without meningitis and without cord symptoms clinically. One of these writers[26] had previously (1904) described cases of dementia præcox in which there were no changes in the vascular connective tissue elements of the brain but only in the neuroepithelial elements. There were no leucocytes, no diapedesis, no hyperemia, no proliferation or degeneration of the walls of the vessels. He concluded from his studies that dementia præcox was a degenerative disease of the neuroepithelial elements of the brain and cord without involvement of the vascular connective tissue elements and that where the latter appeared to be involved, the involvement was due to intercurrent disease. In 1909 Moriyasu[26] presented nine cases, studied in extenso, in which he showed that the fibrils were fragmented and distinctly decreased in number. Changes in the ganglion cells were definite and distinct but, in accord with all workers, the changes in the ganglion cells were not characteristic of dementia præcox. Vascular changes were not significant. The glia nuclei were increased about the blood vessels, especially in the white matter and there was satellitosis about the pyramidal cells. He also says that changes in Clarke's column of cells in the spinal cord are constant. No plasma cells were found in any of his cases. He studied seven females and two males, ranging in age from twenty-five to fifty-three. The duration of the disease was from a few days in one case to two

years in one case. One died of erysipelas, two died suddenly, cause not given, and the cause of death was not given in the other six cases. To have quoted one thorough worker is to have quoted the rest most completely. Klippel and Lhermitte mention a pigment increase in the neuroglia (quoted by Moriyasu[27]). Mondio[28] (1905) says that the changes in the ganglion cells are those seen by others in idiocy and in the intoxications. Obregia[29] mentions chromatolysis and meningeal thickening with proliferation of the cells of the meninges and of the vascular adventitia.

Glia increase both cellular and fibrillar, with changes in the cells and fibrils; pigmentation of the nerve cells and of the glia and pigment lying free in the tissues or about the vessels or in the vessel walls or lumen; the presence of small lymphocytes or of leucocytes; loss of myelinated fibers; degeneration products such as fatty and protogonoid granules; satellitosis and neuronophagia; have all been observed and recorded.

What are the microscopic findings in the frankly delirious cases? the confusional cases? the toxic cases? Perhaps the first good description of that picture is the one given by Jehn[2] in 1877. The vessels showed fatty degeneration and nuclear heaps and pigmentation. There was extravasation of blood and overgrowth of glia. The lymph spaces contained fat and the cell protoplasm showed it also. Next Rezzonico[5] in 1884 showed dilatation of the finest vessels, with fatty degeneration of their walls and emboli made up of groups of micrococci. He noted in his writings that Briand had already, in 1882, found bacilli in the blood in three out of seven cases of acute delirium. What threw many cases out of the delirious group and into the dementia præcox group or what corresponded to it, then as today, was the absence of any notable fever; and albuminuria was only slight. How many times have we seen that ourselves in cases that went rapidly to a fatal termination!

Next, as might be expected, a specific bacillus was described for acute delirium (Bianchi and Piccinio,[30] 1895). But the histological changes found were the same as those found in dementia præcox: clouding of the pia, edema of the brain, adhesions of the meninges, capillary hemorrhages, extravasation of blood pigment, emigration of leucocytes, acute cellular degeneration (Cramer, quoted by Binswanger and Berger,[31] 1901), increase of glia and vascular nuclei (Popoff, quoted[31]), swelling and degeneration of the myelin sheath (Schukowsky, quoted[31]), satellitosis, chromatolysis (Weber,[32] 1904).

What were the general findings in the psychoses by Nissl and Alzheimer and those working at about their time, in and out of their laboratories? Alzheimer,[33] in 1906, remarks that with the same tinctorial methods which enabled us to differentiate general paralysis from senile dementia, etc., we are unable to show differences in the simple psychoses. Pathological changes are not lacking, he states, but who will number the cells or fibers lost? This seems to be his idea of the proper direction for future research in the psychoses. Fat occurs in epilepsy and in many other conditions besides the infections and dementia præcox. Protogonoid substances occur also in amaurotic idiocy (Alzheimer[33]). The neurofibrils, as studied by the Bielschowsky method (Schütz,[34] Jena, 1908), have lost their network arrangement in the cell bodies in dementia præcox, general paralysis, and secondary dementia. Glia proliferation has been observed

in general paralysis, senile dementia, alcoholics, uremic psychosis, and typhus delirium (Nissl, quoted by Alzheimer[35]). Yellow pigment in the cell bodies, first claimed by Campbell[36] to be pathognomonic of senile dementia, was found by Alzheimer[37] to exist also in epilepsy, arteriosclerotic degenerations and in general paralysis. Then Rosental[38] (1913), demonstrated that changes in the glia resembling the ameboid glia, could be produced experimentally by the injection into rabbits of guanidin, sodium oxalate, or of foreign serum into a sensitized animal. Granular degeneration and neuronophagia were also produced. This writer demonstrated, also, that the ameboid glia were certainly not postmortem appearances. A series of non-insane cases studied by Vogt[39] (1901) showed degeneration of cells, increase in neuroglia, and exudate in non-insane cases. Tuberculosis, according to him, shows chronic changes in the nerve cells generally, and may show increase in the glia.

With the case of pseudotumor cerebri (Rosental,[22] 1911), there appeared the acute Nissl reaction so often seen in the infectious processes, and also ameboid glia, satellitosis, protogonoid granules, and lipoid inclusions in the cells, just as we have seen in all the conditions presented in this paper.

The earliest and, perhaps, the best statement of the meaning of all this, is one written in 1898 by Juliusberger and Meyer.[40] They were of the opinion that the changes found were "evidence of abnormal life processes in the cell" and this simple statement can scarcely be excelled today. We can add just one thing to it, perhaps, and that is to state a little more clearly just what those abnormal life processes are and just a little as to how they may be effected. We have done this when we consider the reactions of the human organism, with its fats, carbohydrates and proteins, to the foreign substances which invade it, whether or not as bacterial protein or fat, and when we add to our considerations the susceptibility of the individual, especially whether or not he is hypersusceptible. We were all interested, I am sure, when we read in the Journal[41] that the typical histological picture found in the organs in tuberculosis, had been produced experimentally by the injection of the waxes from the bodies of tubercle bacilli into several different laboratory animals. The whole of pathology itself seems rapidly to be resolving into just such considerations and possibilities.

The conclusion from the above work that certain cases of dementia præcox may be of toxic or infectious origin is almost foregone. With this introduction, I wish to present four cases from the records of the Worcester State Hospital, in which the toxic factor was a large one but was not recognized until autopsy or until certain special tests were applied, namely, the spinal fluid and blood examination by microscopical, chemical, and serological analysis.

The first case was that of a female, W. S. H. No. 23119, age fifty-seven, diagnosis dementia præcox. Onset was at forty-four to forty-nine, variously estimated. She was first admitted to the McLean Hospital in 1903. She had been an efficient worker but gradually came to think that people were talking about her, later expressing the idea that she was boycotted and that people pointed her out on the street. Then she heard the telephone buzzing all night and said that someone kept a lawn-mower going another night. She was finally found on

the roof where she went to get rid of the voices. At the Hospital, her conduct was quiet and natural but she seemed a little depressed and preferred not to talk about her troubles. She was discharged but had to return because the scrub-

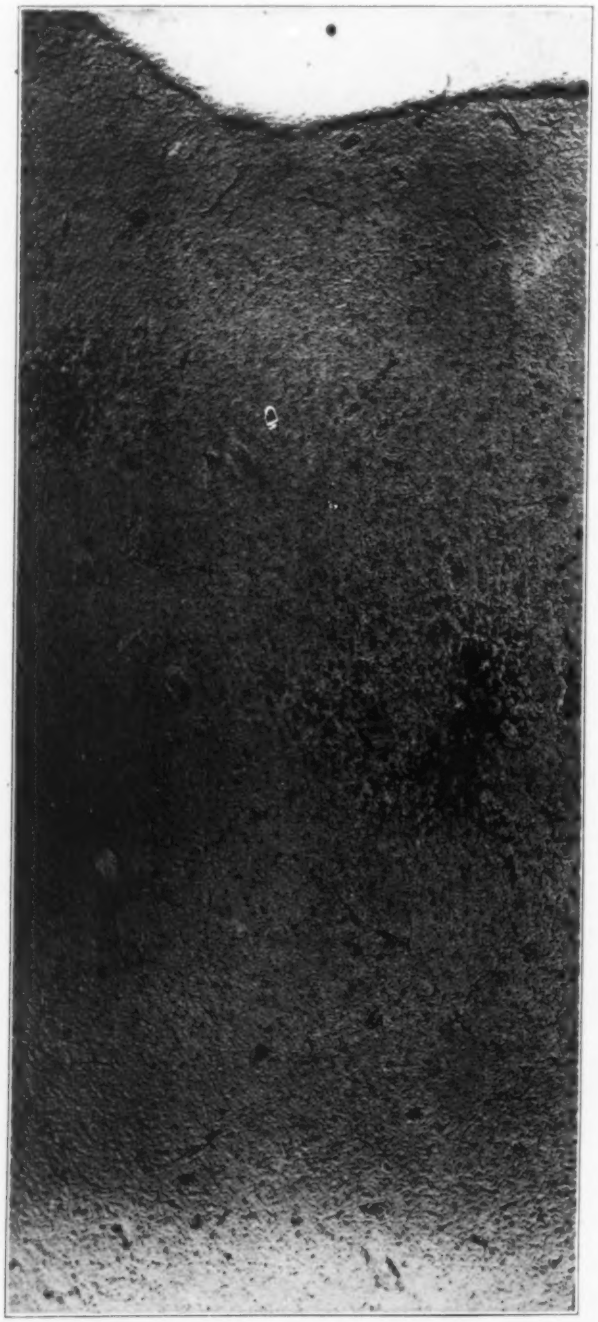

Fig. 1.—Case 1, tubercular paranoid dementia præcox. Cortex of the right superior occipital gyrus, showing two massive processes probably related to the patient's tuberculosis. Section cut 50 micra. Scharlach-R stain. Photograph takes in cortex to white matter.

girl made faces at her, as did the priest in church, and voices dictated to her what she should do and derided her over the telephone. She became exalted and incoherent. She had some insight at first, saying that she could not understand how the voices could be heard, but insisting that she heard them. Physically her condition was good and she gained in weight about six pounds. She left the Hospital again in 1904 and returned in 1908. She was rather more demented than when she left, but physically she complained only of feeling tired all the time. Her weight dropped steadily from about 160 at last admission to about 90 pounds at death in 1915, a period of seven years. The postmortem examination showed adhesions in both pleural cavities, with fluid in the left cavity. Both lungs showed masses of tubercles, many of them coalescing and breaking down to form cavities. There were also irregular, circular ulcers in the ileum near the cecum. No discovery was made of the patient's condition clinically, when an x-ray examination of her chest at the outset would doubtless have revealed it.

The second case was that of a male, W. S. H. No. 26963, of unknown age but thought to be about fifty-two. He was admitted to the Hospital in 1910 and died suddenly in 1915 of coronary sclerosis with occlusion and acute hemorrhagic pancreatitis. He had led rather an irregular life, admitted having had private disease twice and being treated for gonorrhea at Tewksbury. Was told, a long time ago, that he had a chancre. He says he caught the fever at eighteen and his hair came out. He married twice; his second wife was a dissolute woman and was drunk most of the time. She left him about fourteen years ago. Patient admitted arrests and serving sentences and that he drank too much. The onset of his trouble was in 1909, coming gradually and finally terminating in his refusing to pay for a meal at a restaurant one day, on the ground that he owned the place. He was confused and rambling on admission. Said he could hear the voices of his parents and the voice of Jesus. Stated that "when he had his beard on" he could climb a telegraph pole and telephone to anyone. He became irritable, silly, demented. After three years, he said he could still see God and later that his father and mother still talked to him but that he was not bothered any more by it. His physical condition was always good. He took up the work assigned to him and had parole, sweeping up the yards, and so on. He had a scar on the prepuce, a palpable liver and a negative blood Wassermann. The spinal fluid examination was not made. The practice of not taking a Wassermann on the spinal fluid because the blood Wassermann is negative can not be too strongly deprecated, as this case with the scar on the prepuce and the abundant history and the next case show.

The third case was that of a male, W. S. H. No. 28853, age twenty-nine on admission, age thirty at death; total duration about two years. The patient was one of 26 pregnancies; 2 miscarried, 18 died in infancy, 1 died of convulsions, 2 boys and 4 girls still living and one of these has "fits." I cite these facts because there is some question in my mind as to whether the patient was not one of those congenital syphilitics whose disease becomes manifest at a later time than we are in the habit of thinking. (Dr. Abner Post, Neurosyphilis Conference, Grafton State Hospital, 1916.)

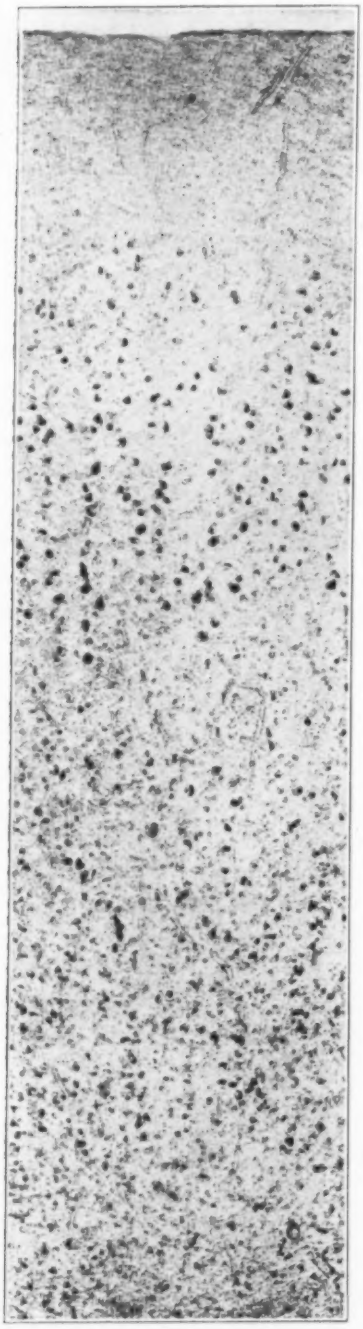

Fig. 2.

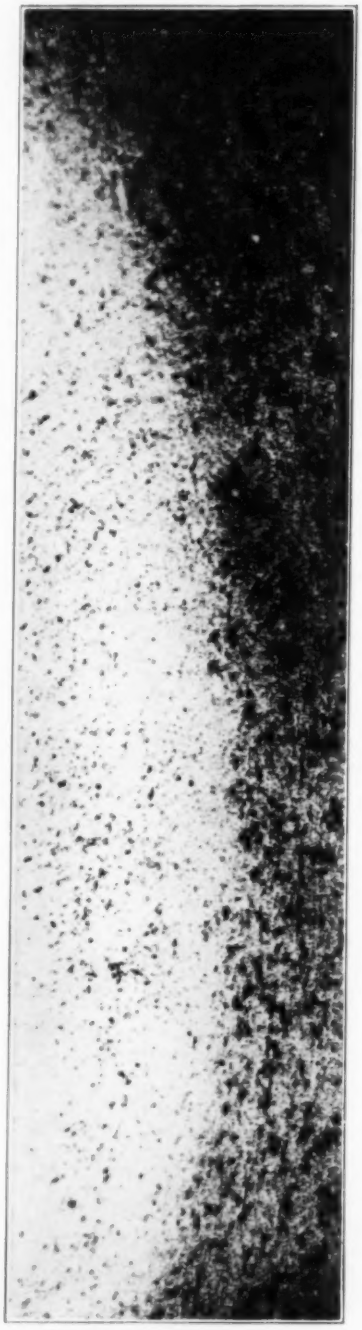

Fig. 3.

Fig. 2.—Case 2, alcoholic paranoid dementia præcox. Cortex of the left supramarginal gyrus, showing the fat to be chiefly in the outer layers of the cortex. Section cut, stained and photographed as in the previous case.

Fig. 3.—Case 3, paretic-like katatonic dementia præcox. Cortex and white matter of the left lingual gyrus, showing the large amount of fat in the white matter and the small amount in the cortex, with the sharp line of demarcation between the two which appeared in many sections. Staining and cutting same as before, but photograph includes only the white and the cortex at the bottom of a sulcus.

About 9 months before admission to the Psychopathic Hospital (No. 2632), the patient had become excessively alcholic and oversexual. Two months before admission he had auditory hallucinations and thought he was about to be killed. He became maniacal, destructive to furniture and went out at night only partially clothed. He would remain from home a week at a time, contrary to his usual habits. On admission, he said he was "confused in his head." He was inaccurate about his recent movements and about the ordinary facts of his life and of his family. He was easily distracted and had exalted ideas about his talents as a singer, demonstrating until he was hoarse. Knee jerks were unequal and absent on the left. Admitted to the Worcester State Hospital, he was at first loquacious, showy, euphoric, but became irritable, sullen, resistive, mute, and had to be tube-fed. Later he had a convulsion, became wildly excited, then mute, untidy and stuporous. At the last he showed typical katatonic rigidity, with legs drawn up and massive, multiple decubitus developing. At the Psychopathic Hospital the provisional diagnosis had been manic depressive insanity, manic phase, then dementia præcox, and finally with the appearance of the Wassermann, general paralysis. The blood was positive. The spinal fluid showed 732 cells and the globulin and albumin were each 3 plus.

Autopsy showed a scar on the corona, there were dense adhesions in the pleural cavities and fresh tubercles or gummata were present in the lungs. The pia was thickened and showed whitish plaques. The brain weighed only 935 grams. The frontal poles were pointed, the right being much smaller than the left. The parietal regions were especially soft. The left cerebellar hemisphere was smaller than the right. The posterior columns of the spinal cord were almost confluent.

The fourth case is that of a negress, W. S. H. No. 3009, age nineteen, who was admitted to the Psychopathic Hospital (No. 5918, No. 6412), on March 20, 1916, transferred to the Worcester State Hospital March 29, and died April 2. On March 15 she began to fail and since she had failed to receive a certain letter from a certain young man, and since she was a mental case, the two facts seemed connected in some hidden manner. But on March 19 she had complained of malaise, anorexia, pain in the epigastrium and later of a "bursting headache." Her temples beat and her neck felt stiff. That evening, while setting the table, she disappeared and was not found until the next morning in an empty room next to her own, where she lay with her throat cut. She slowly recovered from the stupor in which she was found, when she explained that she had been drawing water when her head began to swim and she did not know anything more but that she had felt crazy. Her replies at the Hospital were inaudible, given only on close questioning, and she was stupid, apathetic, and indifferent. March 26 she developed cerea flexibilitas, muttered through her teeth, and retained her saliva. The breath had a foul odor. She said the doctor told her she was going to have a baby, but admits that she had a menstrual period only the week previously. Pulse was 132, temperature 100-101° F. constantly, respiration 20. She became restless, mute, untidy, resistive, at times shouting and at the end picking at the bedclothes. On March 30 there was a trace of albumin, numerous red blood cells, and numerous hyaline and granular casts in the urine. The

sputum was thin, green and purulent, and showed leucocytes and a bacillus morphologically like the influenza bacillus. The postmortem examination was practically negative and the case was reported as one of katatonic exhaustion or

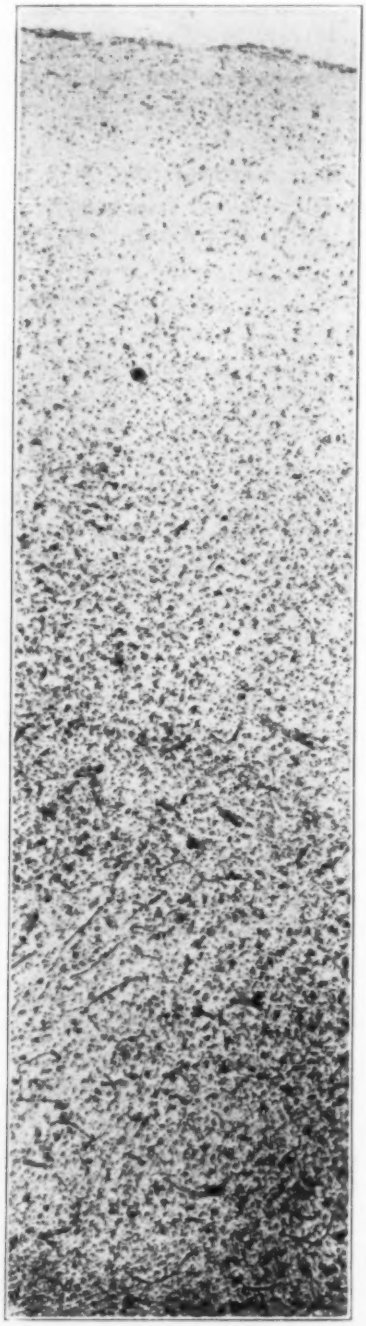

Fig. 4.—Case 4, influenza katatonic dementia præcox. Cortex of the right quadrate gyrus, showing the distribution of the fat in the small elements of the entire cortex, fairly evenly distributed. Staining, etc., as in Cases 1 and 2.

"Hirntod." But cultures taken from the heart's blood at autopsy showed a bacillus which, in its morphology and cultural characteristics, was the influenza bacillus.

Summarizing, we have two cases of the paranoid form of dementia præcox, both of rather long duration, one male and one female. One died of tuberculosis, the other of hemorrhagic pancreatitis and coronary sclerosis. And we have two cases of the katatonic form, both of comparatively short duration. One died of paresis, the other died of influenza. In one case of the four, only, could the mental diagnosis be questioned. The paretic case could be settled only with the Wassermann technic. The paranoid case with the alcoholic history and the history of chancre might be questioned. All but this one died of an infection. In two of these the infection undoubtedly ran parallel to the mental symptoms. In the third, which died of tuberculosis, is it too much to imagine that the mental symptoms also paralleled the physical disease?

The microscopic findings were studied by the photographic method on twenty-four sections from each side of the brain in each case. These were arranged according to what we know of the great functional subdivisions of the brain—the pre-Rolandic and the post-Rolandic, the latter being divided into parietal, temporal and occipital to correspond to general sensibility, hearing, and sight.

The stain used was the Scharlach-R for fat, because it is the most general stain we have for degeneration products of the nervous system and because it photographs so well.

The sections were cut at 50 micra with the idea that, if fat were found, it might present itself in some sort of radial or stratified way which would fail to show in thinner sections. This did not prove, in general, to be the case in this series but the method was carried out, as it appeared logical and gave fair photographs.

In general, the fat was found to be fairly evenly distributed over the cortex, with the exception of that in the alcoholic case. Here it was more marked in the general region of the second to fourth layers, or at least to the layers lying more externally. In the tuberculous case, there was a distinct massive process in several regions. In the paretic case, the fat was more abundant in the white matter, and this more in the post-Rolandic regions, corresponding to the areas that were noted at autopsy to be the softest. The paretic case was the only one showing any considerable fat in the white matter.

A hint has been given in the above at the topographic idea and at the stratigraphic idea. So far as I have been able to determine, only two writers have attempted any definite correlations between disease of cell layers and dementia præcox, or disease of brain areas and dementia præcox. Cotton,[42] as admitted by Alzheimer,[43] was the first to correlate disease of the second and third cortical layers with dementia præcox, mentioning at the same time that the fat occurs over the entire cortex. Southard[44] was the first to claim a relation between disease of the post-Rolandic areas and dementia præcox of the katatonic form and between disease of the frontal areas and the paranoid form. Later, Southard and his coworkers have shown some connection be-

tween lesions of the angular gyrus and katatonia,[45] gliosis of the thalamus and dementia præcox,[46] and cerebellar hemiatrophy and katatonia.[18]

Other writers have laid emphasis in their cases on a predominance of the pathological findings in one layer or another or in one brain area as against another, but no one has made any special claims for these observations before the writers mentioned above. Thus Alzheimer[43] mentioned changes in the deeper layers at first, later pointing out that they occurred in the more superficial layers to a greater extent. Klippel and Lhermitte[47] found the changes more in the zones of association, in the large pyramids of the third layer of cells and in the fusiform cells of the sixth layer of Hammarberg. Dunton,[47] in a case of katatonic dementia præcox dying of pneumonia, found chromatolysis most marked in the fifth layer of Hammarberg. Lubouchine[48] mentions the molecular layer and the layer of the small pyramids; Lannois and Paviot[49] mention the Purkinje cells of the cerebellum; Koller[50] mentions increase of glia in the superficial layers and in the white matter; Elmiger[51] mentions the free edge as being most affected; Orton[52] finds the ameboid changes more in the deeper layers and in the white matter; Sioli[53] finds more change in the upper layers; Mott[54] in the infragranule layers. As for the fibers: Cramer[1] mentions thinning of the interradiary and tangential systems; Weber,[32] the supraradiary network; Eisath-Hall,[55] Meynert's layers. All have support in the shape of corroborative work by other investigators.

Dunton[47] and Maschtschenko[56] claim that the frontal lobes are more affected; Zalplachita,[57] the frontal and central; Orton,[52] that the temporal and occipital are less affected than other parts; but no one has, so far as I can learn, investigated the question of topographical distribution in, and for itself, except the writer mentioned above.

The four cases here presented can add little of a decisive nature to these great questions. Only one case presents anything of interest to the stratigraphic question. That is the case of the paranoid with the alcoholic history, who died of hemorrhagic pancreatitis and his history and physical examination make the diagnosis of dementia præcox somewhat doubtful. However, in his case we do not have to consider the effects of an intercurrent or of a causative infection upon the cell picture, as we do in the three other cases. In his case the fatty changes were more in the outer layers. Topographically, his case was rather indefinite, the fat occurring mostly in the areas of audition and of general sensibility. The fact that the fatty degeneration is rather marked in the temporal regions in this case is especially interesting in view of the continued auditory hallucinations which the patient experienced, but the fact of its absence in other areas may mean either that the cells in those areas are exhausted or that they were not affected, at least at the time of the patient's death. To determine whether they were really exhausted would be an especially interesting research in view of ideas entertained that there is a relation between frontal lobe lesions and paranoid dementia præcox.

The idea that the power of the nerve cells to produce fat has been exhausted in those areas where the fat is not found, is given support by the findings in the second case of paranoid form, dying of tuberculosis. This case

was especially chronic, lasted longer than the first case, and clinically showed much more profound deterioration. From our knowledge of the occurrence of fat in the various pathological processes, we should expect to find an abundance of it here, and yet we find much less than in the first case. The idea gains credence that the fat-producing power is exhausted. In this case there were large masses of fat present, reaching macroscopic size in places, and doubtless connected with the tuberculous processes in the lungs and the intestines, but in general the whole cortex appeared exhausted.

The case of the young katatonic who died of influenza, has a most interesting distribution of the fat in the small elements of the cortex, especially in the glia cells and the blood vessel walls. The blood vessels are especially prominent, also, even the finest capillaries standing wide. The fat is distributed here in all layers and in all areas. It is in the most labile elements, the elements which are the most easily affected according to all writers, and the disease process was so fulminating that the nerve cells themselves have scarcely had time to react. Perhaps this case, together with the two previous ones, may give us some idea as to the fat-producing period of the nerve cell. It is evident that no topographic or stratigraphic ideas could be drawn from this case.

The last case, that of the paretic with katatonic mental picture, is striking by reason of the enormous amount of fat to be seen, and because the fat is confined for the most part to the white matter. The question arises here, as in the cases above, whether the cortex is involved at all or whether it is exhausted. Perhaps we have a type of paresis involving the fibers more especially and the gray matter rather less, just as it has been suggested (Southard[58]) that there are two types of feeble-mindedness, the type with plenty of pathways but little to go over them and the type with plenty of receivers and senders but few wires. The topographical significance in this case is great because the chief degeneration was found in the post-Rolandic regions, corresponding to the katatonic picture presented by the patient. And at autopsy, the especial softness of the parietal areas was noted.

With such an array of pathology as presented in the literature and in the histories and examinations of these patients, one should hesitate to make an unqualified diagnosis of dementia præcox, in the manner in which such diagnoses are made in many hospitals. There are few uncomplicated cases of dementia præcox. The question of a faulty diagnosis, the placing of a patient in the class of dementing psychoses of unknown cause, is often a difficult one to settle, but the attempt should always be made and methods should be added to the diagnostic facilities of most of our hospitals for the insane. Even in this small number of cases, the paretic one would most certainly have been missed had the patient's blood proved negative to the Wassermann examination and if it had been examined from certain of our hospitals. I have repeatedly taken the spinal fluid postmortem, where the examination was refused during the life of the patient on the ground that the blood was negative, and I have repeatedly found it positive to the Wassermann, chemical, and microscopical examination. In the case of the katatonic, the true picture would never have been revealed,

had it not been for the extensive bacteriological examination postmortem. Morphology is not enough to identify an organism. Extensive culturing, before and after death, and a microscopic examination of the tissues at autopsy, with the well known stains for bacteria, will often yield results in many cases of our so-called dementia præcox. Do not forget to stain for the tubercle bacillus. And soon we will come to a splitting of the dementia præcox group, here in America, into a lot of little groups, each on its own etiological basis. The beginning has already been made in splitting off those with a positive Wassermann reaction and other positive tests on the spinal fluid. Who knows how many are caused by influenza or tuberculosis or alcohol?

Beyond this talk of the individual case stands the interest in the group and for most of us, this interest crystallizes into the demand for the *why* of the mental picture. Like the why in any question concerned with the human body, we must go for the solution to physiology, before we can understand abnormal functionings. The brain is divided into several great regions according to this point of view, and hence our necessary interest in topography. On the mental side, in recent years, great efforts have been made to get at the roots of the ideas entertained by psychopathic subjects. Such efforts have rapidly departed from the teachings of the original founders and have drifted into a miserable, nondescript state which I have been tempted to call "neo-mysticism." Such a state was far from the minds of the founders, I am sure, for they said, in speaking of hysteria,[59] that the mechanisms which they had discovered could develop only on a constitution predisposed. And I take it that some of our ultra-moderns, even, are coming around that way, for I note that some account for their lack of success with the method by saying that the patient "did not have the 'stuff' in him," meaning by that, I suppose, that the patient was defective from the start. What makes the whole thing so mystical is not that its advocates deny the operation of physical elements, but that they behave as if they did. It is of little moment for one to admit that there is a constitution behind the patient's trouble, if in the next moment he tries to right the patient's difficulty by letting loose some pent-up ideas from the subconscious personality of the individual, such ideas always to be sexual in nature. This I take to be the gist of the difference between "neo-mysticism" on the one hand and Freudianism of the true sort with its psychoanalytic method, on the other. Some writers and workers have come to recognize this difference and so we see the attempt being made to resolve character into other elements than the sexual alone, and I think a truer picture will be presented—though we run the risk of being suspected of having certain complexes ourselves, you know, by trying thus to avoid the issue.

But what has come out of all this is a method, and the method can be of value to the anatomist. If this method can resolve the faulty character into its elements and these elements can be correlated with the abnormal functioning of known physiological regions, we have an extremely valuable method, indeed. Something of this sort might be expected from the introspective method of experimental psychology. By introspection, under experimental conditions, it is possible to resolve complex feelings, emotions, and ideas into simpler

elements which are visual, auditory, kinesthetic, etc., but we can never get patients to introspect under experimental conditions. Is not the psychoanalytic method the one to be used in resolving the patient's experiences into elements? Something may also be expected to come from the study of the behavior in the sense used by the experimental psychologist whose special field is the behavioristic side of physiology. But the study of the behavior of an insane individual is aided by the explanations of that individual, if those explanations can be analyzed and how can they be analyzed at the present time, except by the psychoanalytic method? Let us take, for example, the sign so often seen in dementia præcox, confusions of all sorts, and in the deliria—the removing of the clothing. The patient is said to be denudative. The reasons for the removal of the clothes under improper conditions, may be various. One may say it is a sign of exhibitionism, another that the clothes irritate the patient because the skin is hypersensitive, and so on almost *ad libitum*. But we may gain something, if we ask the patient about it. He may give a valuable answer directly or we may arrive at a valuable conclusion as to the reason by piecing his replies together, as the psychoanalytic method does.

Apropos of asking the patient questions, I am reminded of a striking incident which was observed during an intraventricular treatment for paresis. The patient became restless just as the needle was passing through the cerebral substance. Asked what the matter was, the patient replied that he would be all right, if the doctor would stop "making his mouth (patient's) fill up with spit"—and that his mouth was actually filling up with saliva was not imagination. Beside giving the reason for his restlessness, his reply gave a cue to a second very important point, that a cerebral injury may affect a gland-secretion. Ceni[60] has also shown changes in the cells of the testicles of roosters by subjecting them to cerebral injury.

The suggestion to use the psychoanalytic method along truly Freudian lines and not in the hazy way in which it is now being applied by his successors, for the most part, should be made now. But the application of the psychoanalytic method in this new way will have to wait until those using it recognize that there is something more beneath character than sex and that there is something more in personality than character alone. I mean by this that personality includes much more in its connotation than the word character includes. And only when these two are recognized, will the psychoanalytic method be of value for the topographical study of the cortex lesions of the insane and for the correlation of those topographically distributed lesions with the mental picture presented by the patient.

The requisites for future advance, then, are the recognition of unrecognized work: recognition of the fact that the central nervous system of dementia præcox patients gives evidence of abnormal life processes in the cells; that the same changes are present in the intoxications and the infections, in the confusions and the deliria; that there are methods at hand for diagnosis which are not being used; and that the diagnosis is often difficult and often wrong and will often be wrong when we have exhausted all our methods, but an intelligent attack will have been made.

CONCLUSIONS.

1. That cases of dementia præcox, of confusional insanity, or of delirium, of pseudotumor, and of various other mental conditions have pathological changes which are similar.

2. That it is quite apropos to assume that certain cases of dementia præcox are due to infectious or toxic processes, in proof of which four cases are introduced, one of which is definitely syphilitic, one is alcoholic and possibly syphilitic, one is tubercular, and one is a case of influenza of fulminating type.

3. That cases which can be detected are being missed because of the lack of application of diagnostic methods. As an example, the refusal to permit a spinal puncture where the blood Wassermann is negative is especially decried.

4. That topographic studies are next in order, as offering a logical direction of research in solving the why of the mental picture—later to be followed by stratigraphic studies.

5. The idea is suggested that the psychoanalytic method may reduce the mental condition to elements which can be correlated with lesions topographically or stratigraphically disposed.

In conclusion, I wish to express my thanks to those who have shown their interest in this work, of whom there are many, and also to my Laboratory Assistant, Julius H. Stean, who assisted materially in making the sections and the photomicrographs.

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ON THE POSSIBLE DERIVATION OF THE ACTIVE PRINCIPLE OF THE POSTERIOR LOBE OF THE PITUITARY BODY FROM THE TETHELIN PRODUCED BY THE ANTERIOR LOBE*

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TWO views may be said to exist with regard to the place of formation of the active substance of the posterior lobe of the pituitary body: (a) that it is formed in the posterior lobe and may be a primary product of nervous tissue secretion; (b) that it is derived from the secretion of the anterior lobe which passes in part via the pars intermedia into the posterior lobe and so to the cerebrospinal fluid. Neither of these views has received sufficient experimental support to secure unequivocal adoption.

The former view is supported by a large amount of experimental work, the greater part of which shows that the active principle which on injection causes a marked rise in blood pressure, increase in the secretion of urine and milk, and contraction of smooth muscle, especially the uterus,[1] is found only in the posterior lobe while, as has been pointed out in the previous communication, neither extracts nor the pure substance tethelin, obtained from the anterior lobe, possesses these properties. To support the second view we possess merely indirect evidence. Of the two parts of the pituitary body the anterior apparently plays the more important role. Its secretion is necessary for the maintenance of life.[2] The work of Paulesco[3] confirmed by Crowe, Cushing and Homans[4] showed that extirpation of the whole pituitary body is fatal, this being entirely due to the loss of the anterior lobe since removal of the posterior lobe gave negative results. This may mean either that the secretion from the posterior lobe is not necessary for the maintenance of life or that conversion of a part of the secretion from the anterior lobe into posterior lobe substance can take place even after extirpation of the latter gland. Herring[5] points out that skates possess no posterior lobe.

Cow[6] found that in the cat definite channels of communication exist between the ventricular cavity in the infundibular stalk and spaces in the anterior lobe. In several extensive investigations, Herring[7] found that a uterine contracting substance can be obtained from the pars intermedia. He believes that the active principle of the posterior lobe is derived from cells of the pars intermedia. The epithelial cells of the pars intermedia secrete a colloid material which passes into the pars nervosa. The hyaline bodies break down liberating either a clear hyaline material or at times granules. Breaking down of the cells from pars intermedia presumably takes place in two stages; this would explain the formation of possibly two active substances one of which acts primarily on blood pressure and the other stimulates contraction of smooth muscle, especially the uterus. The presence of a colloid material in pars intermedia, also found in pars nervosa suggests a possible derivation of the active principle of the posterior lobe externally

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although Fenger[8] finds that the colloid masses secreted between the anterior and posterior lobes do not possess uterine contracting power.

Although several observers, among them Aldrich,[9] Engeland and Kutscher,[10] and Führer[11] have reported the isolation of pure substances from the posterior lobe, no single pure substance of definite chemical nature has been isolated to which can be attributed the properties shown by posterior lobe extracts. This, of course, may be attributable to the presence of several physiologically active substances in the posterior lobe. The work of Dale and Laidlaw,[12] and Barger and Dale,[13] showing the specific action of β-iminozolylethylamine in producing contraction of the isolated uterus; the work of Ackermann,[14] Mellanby and Twort,[15] Windaus and Vogt,[16] and Pyman[17] showing the constitution of this substance and its relation to histidine; and the findings by Aldrich[18] of histidine-like substances in the posterior lobe; and more recently the isolation by Robertson of a definite chemical substance containing the iminozolyl radicle from the anterior lobe; these facts point very strongly to the supposition that the uterine contracting principle of the posterior lobe may be a resultant product from the splitting of the substance secreted by the anterior lobe.

Through the kindness of Professor T. Brailsford Robertson in supplying us with generous amounts of tethelin and giving us his unfailing interest, we were enabled to test this hypothesis and attempt if possible to split this substance, which on repeated tests proved to have no action in causing contraction of the isolated uterus of the nonpregnant cat or guinea pig, into products simulating posterior lobe extract in its action. Previous experiments with enzymes and bacteria gave negative results. We were then led to test the product resulting from the action of barium hydroxide on tethelin whereby the fatty acid radicle is split off, this reaction having previously been noted by Robertson.[19] In using the barium-split product we were well aware of the experiments of Guggenheim[20] who found on treating pituglandol with NaOH, $Ba(OH)_2$, and PbO that inactivation of this substance had taken place, as well as those of Führer[11] who used barium in the isolation of pure substances from the posterior lobe.

On addition of $Ba(OH)_2$ solution to a solution of tethelin an immediate flocculent precipitate is formed which quickly settles leaving the supernatant fluid perfectly clear but still possessing a straw-yellow color. Warming facilitates the flocculation. The excess of barium is precipitated with CO_2 and filtered off. Soluble barium bicarbonate is removed by evaporation of the solution to a small volume; the barium is precipitated as the carbonate and filtered off. The filtrate is perfectly clear and possesses a light yellow color and retains the odor characteristic of tethelin solutions. Tests indicated no barium. The entire amino-nitrogen of the tethelin is found in this solution.

Experiments with the solution of tethelin-split product on the isolated uterus of virgin guinea pigs suspended in Locke and Ringer solutions were carried out in essentially the manner described by Dale and Laidlaw.[21] Difficulties attributable to hypersensitive uteri as noted by these authors were likewise experienced by us. Such uteri were rejected. Addition of tethelin-split product in doses given on the chart uniformly caused contraction; this could be repeated with the same muscle after washing in Locke solution and allowing it to come to rest. That

this action was not attributable to the action of tethelin or contamination by posterior lobe substance was repeatedly shown in control experiments. Neither could this effect be attributable to traces of barium in the solution since control experiments with solutions containing small amounts of barium also gave negative results. All experiments in which no uterine contraction was obtained on addition of the test substance were controlled by addition of either posterior lobe extract or ergamine which resulted in the usual contractions. A number of tethelin-split product preparations were made at different times and in all cases contraction was noted.

Experiments were likewise made to study the effect of the split product on the blood pressure of rabbits under ether anesthesia. As seen from Fig. 2 a slight but perceptible rise of blood pressure follows the injection of this substance. However, no preliminary fall is noted. With very dilute pituitary extract solutions small rises of blood pressure without a preliminary fall were observed and the effect could be repeated several times. Administration of larger doses of the same extract gave a preliminary fall followed by a rise.

While our experiments apparently indicate that we have split tethelin into products among which is a substance resembling in its action the active substance secreted by the posterior lobe, we are by no means certain that our method is the best for accomplishing this reaction or for obtaining a pure product. Since the nitrogen content of tethelin is low (2.58%) and that of β-iminozolylethylamine high (38%), the derivation of this latter substance from the former can yield only a small proportion. The delicacy of the uterine test as a means of detecting small amounts of this product is apparent.

We believe from the evidence presented that the active substance of the posterior lobe of the pituitary body is largely, or in part, derived from a splitting of the substance which is a product of the secretion of the anterior lobe and which contains an iminozolyl radicle.

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STUDIES ON THE PROPERTIES AND ACTION OF TETHELIN*

By Carl L. A. Schmidt, Ph.D., Berkeley, Calif.

THE results of numerous studies by various workers indicated the importance of the anterior lobe of the pituitary body as a growth factor, and showed that extracts of this lobe are relatively inactive physiologically, as contrasted with the extreme activity of extracts of the posterior lobe. However, it was not until the isolation of a definite chemical substance, tethelin, by Robertson[1] that the properties and action of the growth-controlling principle of the anterior lobe of the pituitary body could be more fully studied.

Tethelin is described by Robertson as a cream-colored substance which is readily obtained in powdered form. It is extremely hygroscopic and for that reason is best kept in vacuum tubes. The substance is soluble in water, ethyl alcohol, ether, chloroform and carbon tetrachloride, but insoluble in a mixture of one part by volume of absolute alcohol and one and one-half parts of dry ether. Its content of phosphorus is 1.14 per cent, nitrogen 2.58 per cent, of which one-half or 1.24 per cent is in the amino form, this being increased on complete hydrolysis (conversion of imino to an amino group) to 1.83 per cent or three-fourths of the total nitrogen. The presence of an unsaturated fatty acid is indicated by a saponification value of 87 milligrams of KOH per gram of substance and an iodine value of 33.2 per cent. Tethelin contains an iminazolyl radicle which indicates that possibly the physiologically active substance of the posterior lobe may be derived from it. On complete hydrolysis with barium hydroxide, followed by hydrolysis with dilute sulphuric acid, one of the decomposition products obtained is inosite.

Physiological experiments conducted by Robertson show that certain of the characteristic reactions produced by extracts of the posterior lobe—rise of blood pressure and pronounced diuresis—are not brought about by tethelin. On the contrary, intravenous injection produces a slight and transient fall in blood pressure and a slight increase in the amplitude of the heart beat. These results agree with the experiments of Hamburger,[2] Lewis, Miller and Mathews,[3] Herring,[4] Howell,[5] and others working with anterior lobe extracts.

Robertson[6] also carried out extensive investigations to determine the effect of tethelin on the growth of white mice. He found that administration of tethelin produces a marked retardation of the first portion of the third growth cycle, followed by acceleration of the latter portion of the same cycle. These results are in agreement with the observations of Aldrich,[7] Schäfer,[8] Wulzen,[9] and Robertson[10] on feeding anterior lobe to experimental animals. Cholesterol[11] was found to have a like effect on the growth of mice, although larger quantities are required. Tethelin given hypodermically to rats was found by Robertson and Burnett[12] to increase the rate of growth of the Flexner-Jobling carcinoma, and,

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likewise, to have the tendency to form metastases. In these respects the effects produced by tethelin were similar to those produced by anterior lobe.[13] Cholesterol[14] also produces a like effect. The action of tethelin, as well as other lipoids, on growth are those of a catalyser though the mechanism whereby such catalysers act is not known. Robertson[15] has also investigated the action of tethelin as an accelerator of tissue repair and found that it has a marked stimulating action on the healing of wounds.

On account of the importance of tethelin, as shown by the work of investigators previously cited, and its possible application as a therapeutic agent, it was considered of interest to study the properties and action of this substance further, particularly along the lines indicated by the subsequent headings. Reference to this work has already been made by Robertson.[16] The tethelin used for these

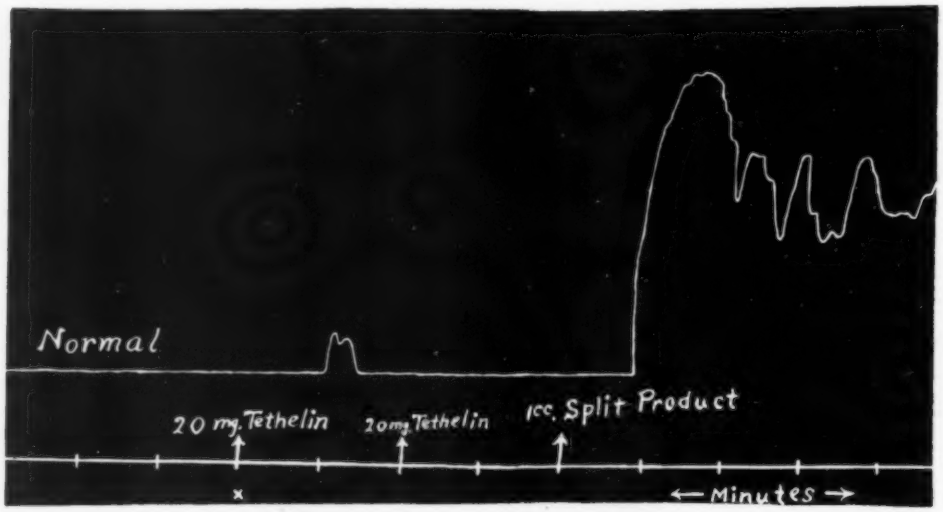

Fig. 1.—Showing effect of tethelin and tethelin-split product on the isolated guinea-pig uterus. 1 c.c. split product =○= to 20 mg. tethelin.

experiments was generously supplied to me by Professor Robertson to whom I wish to express my thanks.

ANTIGENIC PROPERTIES.

Normal rabbits Nos. 843 and 850 were given six intravenous injections of 50 mg. each of tethelin dissolved in salt solution over a period of two weeks and bled ten days after the last injection. Alexin-fixation experiments, using one quarter of the minimum inhibiting dose of antigen and doses of rabbit serum of 1/10 cubic centimeters, were carried out in the usual manner. No fixation was obtained.

Four guinea pigs were given doses of tethelin, varying from 5 to 50 mg., intraperitoneally, and three weeks later each was given a second dose of 50 mg. Observations of the body temperature were made in a similar manner to the method used by Wells and Osborne[17] in their studies on the biological reactions of proteins. Only slight changes in body temperature—not greater than observed

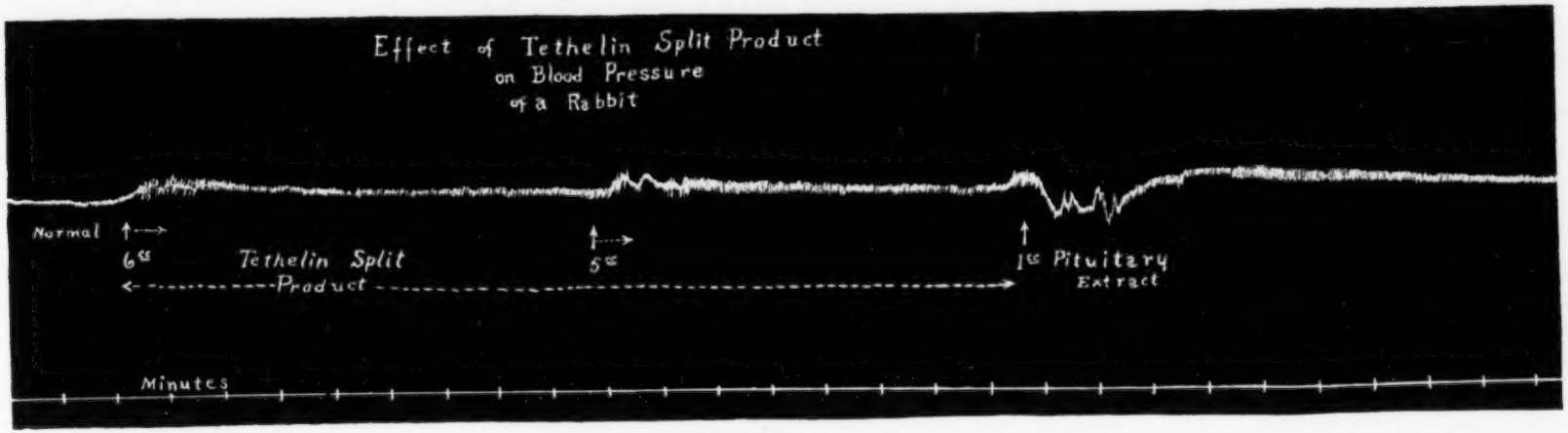

Fig. 2.—Showing effect of tethelin-split product and posterior lobe extract on the blood pressure of a rabbit under ether. 1 c.c. split product ═◇═ to 20 mg. tethelin.

on injection of a similar dosage into a normal animal—were noted. The substance is likewise nontoxic; 100 milligram doses can be given intraperitoneally to a guinea pig without the animal's showing toxic symptoms.

These experiments, showing that tethelin is nonantigenic, are in agreement with the majority of the work on lipoids cited by Landsteiner[18] and the more recent work of Fitzgerald and Leathes[19] and Thiele and Embleton.[20] Adrenalin likewise possesses no antigenic properties, as shown by the work of Elliott and Durham.[21] The characteristic febrile response noted by Crowe, Cushing and Homans[22] on injecting boiled anterior lobe emulsions in states of experimental hypopituitrism can not be attributed to anaphylactic shock (this possibility was pointed out by them) produced by injections of the active principle of the anterior lobe.

The work of various observers, showing that the antigen used in the Wassermann test for syphilis can be wholly or in part replaced by artificial antigens,[23] such as cholesterol, lecithin, fatty acids, etc., led to the attempt to substitute tethelin for the usual antigen used in the test. Through the courtesy of Miss Grace A. Macmillan of the State Hygienic Laboratory, I was supplied with a number of sera and spinal fluids, which had previously been found by her to be triple positive. These tests carried out with the usual technic, using one quarter of the minimum inhibiting dose of tethelin as antigen and 1/10 c.c. of the luetic sera, showed no inhibition of hemolysis. Tethelin is, therefore, incapable of acting as the antigen in the Wassermann test.

EFFECT ON BLOOD PROTEINS.

The effect of the injection of various substances, such as proteins, bacterial toxins, bacterial vaccines and living virulent bacteria, on the proteins of the blood

TABLE I.

EFFECT OF INJECTING 100 MG. TETHELIN INTRAVENOUSLY ON THE PROTEINS OF THE BLOOD SERUM OF RABBIT NO. 845 ♀. INITIAL WEIGHT 3 KILOS. ANIMAL LOST 60 GRAMS DURING EXPERIMENT.

Day of Experiment	Leucocyte count	Non-Protein %	Albumin %	Globulin %	Total Protein %	Albumin calculated as % total Protein	Globulin calculated as % total Protein	Protein Quotient
1	10700	1.3	5.2	1.5	6.7	78	22	3.5
2	.....	..	..	..	..	..	..	..
3	8800	1.3	4.4	1.6	6.0	73	27	2.7
4	11400	1.3	5.0	1.4	6.4	78	22	3.5
5	11800	1.3	4.6	1.6	6.2	74	26	2.8
6	11300	1.3	4.6	1.8	6.4	72	28	2.6
Averages		1.3	4.8	1.6	6.3	75	25	3.0
6	100 mg. tethelin intravenously at 10 A.M.							
6-4 P.M.	12800	1.4	4.7	1.5	6.2	76	24	3.2
7	10700	1.3	4.6	1.6	6.2	74	26	2.9
8	8400	1.2	4.5	1.8	6.3	71	29	2.4
9	....	..	..	..	..	..	..	..
10	10800	1.3	5.2	1.4	6.6	79	21	3.8
11	8000	1.4	4.3	1.9	6.2	69	31	2.2
12	8600	1.3	4.4	2.0	6.4	69	31	2.2
Averages		1.3	4.6	1.7	6.3	73	27	2.8

serum has been the subject for extensive investigations in recent time by Rowe,[24] Righetti,[25] Hurwitz and Meyer,[26] and Schmidt.[27] The effect of tethelin on serum proteins has also been investigated, the determinations being carried out according to the micro-refractometric method of Robertson.[28] As seen from the following results, the injection of tethelin is without effect (Table I, II and III).

TABLE II.

EFFECT OF INJECTING 100 MG. TETHELIN INTRAPERITONEALLY ON THE PROTEINS OF THE BLOOD SERUM OF RABBIT NO. 846 ♀. INITIAL WEIGHT 2380 GRAMS. ANIMAL GAINED 60 GRAMS DURING EXPERIMENT.

Day of Experiment	Leucocyte count	Non-Protein %	Albumin %	Globulin %	Total Protein %	Albumin calculated as % total Protein	Globulin calculated as % total Protein	Protein Quotient
1	11000	1.3	3.8	1.8	5.6	68	32	2.1
2	.....	..	..	..	..	..	..	..
3	14300	1.3	3.7	2.2	5.9	63	37	1.7
4	11800	1.3	4.4	1.8	6.2	71	29	2.4
5	12400	1.3	4.0	2.1	6.1	66	34	1.9
6	11700	1.3	4.4	1.6	6.0	73	27	2.7
Averages		1.3	4.1	1.9	6.0	68	32	2.2
6-10 A.M.	100 mg. tethelin intraperitoneally.							
6-4 P.M.	10000	1.2	4.5	1.4	5.9	76	24	3.2
7	11100	1.3	3.6	2.1	5.7	63	37	1.7
8	11300	1.2	3.9	2.1	6.0	65	35	1.9
9	.....	..	..	..	..	..	..	..
10	10600	1.3	4.8	1.3	6.1	79	21	3.8
11	9800	1.4	3.9	2.4	6.3	62	38	1.6
12	11800	1.3	4.2	1.8	6.0	70	30	2.3
Averages		1.3	4.1	1.9	6.0	69	31	2.2

TABLE III.

EFFECT OF INJECTING 100 MG. TETHELIN SUBCUTANEOUSLY ON THE PROTEINS OF THE BLOOD SERUM OF RABBIT NO. 847 ♀. INITIAL WEIGHT 2470 GRAMS. ANIMAL GAINED 200 GRAMS DURING EXPERIMENT.

Day of Experiment	Leucocyte coun.	Non-Protein %	Albumin %	Globulin %	Total Protein %	Albumin calculated as % total Protein	Globulin calculated as % total Protein	Protein Quotient
1	8800	1.3	4.2	1.6	5.8	72	28	2.6
2	....	..	..	..	..	..	..	..
3	7200	1.3	3.5	2.3	5.8	60	40	1.5
4	7600	1.3	4.0	1.8	5.8	69	31	2.2
5	8300	1.3	3.4	2.2	5.6	61	39	1.6
6	9400	1.2	4.5	1.5	6.0	75	25	3.0
Averages		1.3	3.9	1.9	5.8	67	33	2.0
6-10 A.M.	100 mg. tethelin subcutaneously.							
6-4 P.M.	10100	1.3	4.2	1.2	5.4	78	22	3.5
7	8000	1.3	3.9	1.7	5.6	70	30	2.3
8	7200	1.3	3.2	2.2	5.4	59	41	1.4
9	....	..	..	..	..	..	..	..
10	7700	1.3	4.2	1.5	5.7	74	26	2.8
11	7200	1.3	3.5	2.2	5.7	61	39	1.6
12	7500	1.3	4.2	1.7	5.9	71	29	2.5
Averages		1.3	3.9	1.8	5.6	69	31	2.2

EFFECT ON BLOOD COUNT.

The function of tethelin as a stimulator of the growth of granulation tissue in wounds is that of a catalyser of growth. It seemed possible that the action might consist in the production of an increased leucocytosis. That tethelin has no striking effect on the production of an increased leucocytosis is shown by the following experiments (Table IV).

TABLE IV.

EFFECT OF THE INTRAVENOUS INJECTION OF 100 MG. TETHELIN ON THE LEUCOCYTE COUNT OF RABBIT T. ♂.

TIME.	LEUCOCYTE COUNT.
9:00 A.M.	12300
9:30 "	100 mgs. tethelin intravenously.
10:00 "	11300
10:30 "	9600
11:05 "	10100
11:30 "	14700
12:08 P.M.	16200
12:40 "	11800
1:10 "	12600
1:43 "	11700
2:10 "	10000
2:40 "	10400
3:10 "	12200
3:45 "	10200
4:20 "	9700
5:20 "	12700

The effect of tethelin on the leucocyte count of rabbits under operative conditions was likewise determined. Two rabbits of practically the same weights were operated on for me by Dr. E. S. May. A four inch skin incision on the abdomen of the animal was made under nitrous oxide anesthesia. Rabbit No. 848 received 100 mg. of tethelin subcutaneously just after the operation, while No. 849 received none. The results are shown in Table V.

TABLE V.

TIME.		LEUCOCYTE COUNT.
	Rabbit No. 848.	
Previous day	9:00 A.M.	8000
Day of operation	9:30 "	8100
"	10:30 "	Operated—100 mg. tethelin
"	2:30 P.M.	7100
"	5:40 "	7200
Following day	10:00 A.M.	6700
	Rabbit No. 849.	
Previous day	9:00 A.M.	10,200
Day of operation	9:30 "	13,600
"	10:15 "	Operated—no tethelin
"	2:30 P.M.	16,200
"	5:40 "	12,800
Following day	10:00 A.M.	9,900

The effect of a 200 milligram dose of tethelin administered subcutanenously on the leucocyte count of human subject T.B.R. was also studied with the following results (Table VI).

TABLE VI.

TIME.		LEUCOCYTE COUNT.
Day previous to injection	10:30 A.M.	8400
"	6:00 P.M.	7700
Day of experiment	11:30 A.M.	8100
"	11:45 "	200 mg. tethelin subcutaneously
"	2:00 P.M.	Ring of hyperemia was noted, which disappeared shortly afterwards
"	3:40 "	8500
"	6:15 "	8900
Following day	11:00 A.M.	7200

No temperature change or symptoms were shown following the injection of tethelin. Differential counts likewise showed no appreciable change from the normal. That the slight increase in the leucocyte count following the intravenous injection of 100 mg. of tethelin shown by rabbit T ♂ can not be attributed to a specific effect of tethelin is shown by the work of Hamburger and Reufs[29] and Aschenheim,[30] who obtained similar increases of leucocyte counts on injection of proteins, foreign sera, and other substances.

GROWTH OF BACTERIA.

Certain bacteria can grow on a medium containing one per cent tethelin and a trace of salt. A number of generations of B. coli and B. proteus were grown on such media for a number of generations without the production of gas or indol. B. bulgaricus, however, does not grow on this medium. Gas was produced by B. coli on a medium containing one per cent tethelin and one per cent glucose. Evidently these organisms can derive sufficient nitrogen for growth by breaking down of the complex organic substance.

ACTION OF FERMENTS.

Attempts to split tethelin by the action of ferments gave negative results. Grübler's trypsin, shown to be active by parallel experiments on casein, failed to produce an increase of amino nitrogen after twenty-four hours action on tethelin at incubator temperature. Evidently the complex structure of tethelin makes it resistant to the action of trypsin. In the case of pituitrin it has been observed by Dale[31] that whereas pepsin failed to reduce the pressor or diuretic principle, trypsin reduced the action on blood pressure and urinary flow to nil after a few hours digestion. An active lipase obtained from a pig's liver likewise failed to produce a splitting of tethelin, as judged by increase of titratable fatty acid. Mueller[32] found that cholesterol esters resist saponification by the ordinary lipases, which easily hydrolyze neutral fat. A comparable resistance is evidently shown by tethelin.

That the active principle associated with the posterior lobe of the pituitary body is entirely absent from the anterior lobe was found by a number of observers, previously cited, who have shown that this is true in regard to inability to

produce a rise of blood pressure and diuresis. It has also been shown by Herring[33] that extracts from the anterior lobe do not stimulate the uterus to contract. This has been confirmed with respect to tethelin by a number of experiments on isolated cat and guinea pig uteri. The well known method used by Dale and Laidlaw[34] for the standardization of pituitary extracts was employed. The uteri were suspended in 300 c.c. of either Ringer's or Locke's solution, and amounts of tethelin varying from 10 to 100 mg. added. No contraction was observed. Addition of either pituitary extract or ergamine produced the usual contraction in every instance. This indicates that tethelin possesses none of the characteristic properties of pituitary extracts as well as freedom from contamination by posterior lobe substance. Tethelin which had been subjected to the action of trypsin and lipase likewise failed to stimulate uteri to contract.

SUMMARY.—The properties and action of tethelin, the active principle of the anterior lobe of the pituitary body, have been studied. It was found that tethelin is nonantigenic and nontoxic; hence its use therapeutically is warranted. It can not be used as the antigen in the Wassermann test, has no effect on the proteins of blood serum, does not cause a specific hyperleucocytosis, can be used as a medium for the growth of certain bacteria, is not split by trypsin or lipase, and does not stimulate contraction of the isolated cat or guinea pig uterus.

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MEMORANDUM AS TO THE MEANS OF PREVENTING AND TREATING TYPHOID FEVER, PARTICULARLY IN ARMIES, UNDER THE CONDITION OF WAR*

By Frederick P. Gay, M.D., Berkeley, Calif.

PROPHYLACTIC vaccination against typhoid fever is now acceptably the most important weapon for the prevention and eventual abolition of this disease. Adoption of similar methods to the paratyphoid fevers will unquestionably lead to their disappearance as well. The following statements are presented as a personal impression of how the important facts we already possess concerning vaccination against typhoid may best be applied, and also further suggestions as to lines of investigation that may lead to further advances.

A. PROCEDURES IN ANTITYPHOID VACCINATION WHICH MAY BE REGARDED AS ALREADY SUFFICIENTLY PROVEN TO BE APPLIED.

1. In times of peace and of war armies should be completely immunized against typhoid and paratyphoid fevers by means of vaccination. Every effort should be made, moreover, to extend opportunities for vaccination to the general population, where prophylactic results hitherto have not been so thoroughly good as in armies, owing, at least in some part, to the fact that entire groups of individuals have not been vaccinated. We regard the most successful results of vaccination in the United States Army as due somewhat to the fact that one hundred per cent of the men have been vaccinated. If the entire population became vaccinated, there is reason to anticipate that typhoid fever would eventually disappear.

2. The type of vaccine to be employed in immunization should be uniform. It should be prepared either in a large central laboratory for distribution over the entire country, or might be prepared in several laboratories in different parts of the country under rigid directions and then controlled by a central laboratory. Numerous varieties of typhoid vaccine have been prepared and advocated. It is difficult or impossible to estimate which of these vaccines represents the best preventive against typhoid fever, but that there is a difference in the protective value of one vaccine over another is undoubted. Certain criteria may, however, we believe, be accepted as essential in the preparation and administration of vaccines. The important points in the preparation of the vaccine itself are, we believe, the following:

(a) A typhoid vaccine to be most efficient prophylactically should be polyvalent, containing representative strains of the typhoid bacilli which have been shown to vary, and particularly containing freshly isolated strains in preponderance rather than old laboratory strains of the organism.

(b) The method of killing vaccine may be either by heating to a moderate degree, not above 55° C., or by the admixture of alcohol or ether. I am personally inclined to believe that one of the latter methods is the better.

*Submitted to the National Research Council by Frederick P. Gay, as Member of the Committee on Medicine and Hygiene.

(c) Any vaccine employed for army administration, particularly in times of war, should contain equal parts of typhoid (polyvalent) and of paratyphoid alpha and paratyphoid beta, which should also be compounded of a number of strains. It is probably not necessary to include the paratyphoid vaccines in the immunization of civil communities.

3. Mode of inoculation of vaccine, including dosage.

In addition to the usual procedures of asepsis and choice as to the time of day for administration, care in reference to diet, observation as to the few possible contraindications, a uniform procedure of administering the vaccine should be adopted which should include the following:

(a) The total immunizing treatment should include not less than 3,000 million of each of the organisms, typhoid and the two paratyphoids, employed, which should be administered in equal parts simultaneously. Recent results in Europe lead us to believe that the three vaccines may be given in doses as large as 1,000 million each without any severer results than those obtained by the use of a single organism. Under these conditions three injections would suffice to complete the treatment, but if the reaction is too severe, the dosage could be diminished and a larger number of injections be given, the total amount of bacteria employed being more important than the number of inoculations.

(b) The injections should be given on alternate days, a method which would hasten the time of protection, facilitate the completion of inoculations of large numbers, and will apparently produce as lasting immunity as vaccinations at longer intervals.

4. Methods should be taken to test the lack of immunity in vaccinated individuals.

We believe that the typhoidin test offers an indication of failure of the individual to respond properly to vaccination when the test is negative and thereby serves as an indication for revaccination. The test should not be employed as a means of insurance of absolute protection against typhoid fever, which could probably never be assured. We suggest, therefore, that every vaccinated individual be tested one month after completing treatment by the typhoidin test, which, if negative, indicates need of further injections. Each individual should further be tested at yearly intervals in a similar manner.

B. SUGGESTED LINES OF INVESTIGATION IN ANTITYPHOID IMMUNIZATION.

1. Tests of the comparative protective value of sensitized vaccines.

We believe that sensitized vaccines give indications of protecting better against typhoid fever than unsensitized vaccines. We suggest, then, that it would be thoroughly justifiable and of scientific value to vaccinate in an army certain parts of units with sensitized instead of with unsensitized vaccine in the same doses, so as to test under the subsequent conditions of like exposure the relative protective value of the two methods. This procedure could not be recommended if there were not sufficient evidence to lead us to believe that sensitized vaccines are at least as protective as unsensitized.

2. If similar groups of men are vaccinated by two or more methods, a subsequent study of the presence of antibodies in their blood and of typhoidin re-

actions would be of great value as correlated with their actual protection against typhoid fever.

3. It has been asserted that the typhoidin test is not absolutely specific in that typhoid vaccinated individuals may give a positive reaction with a similar preparation of paratyphoidin alpha. We regard this fact, if true, as in no way militating against the use of the reaction as indicating revaccination. It is important, however, to test out how far typhoid vaccinated individuals will respond to extractives, not only of paratyphoid but of other bacteria, and the similar behavior of individuals that have been vaccinated against paratyphoid as well as typhoid organisms. (An investigation of this problem is already under way in this laboratory.)

C. TREATMENT OF TYPHOID FEVER.

A few cases of typhoid fever will unquestionably still occur in spite of the best methods of prophylactic immunization that can at present be devised. These cases have been present even in the relatively successful results that have attended vaccination in the United States army, and have increased during the recent conditions of greater exposure on the Mexican border. In actual warfare they would be still further increased, as is evidenced by the 1500 or more cases that have occurred in the British army during the first two years of the war. It is important that these cases should be segregated as soon as diagnosis is made, and treated. We regard the recent results with the intravenous injections of vaccine, particularly of sensitized vaccine, as not only promising but as indicated in all cases of typhoid fever, as shortening in the majority of cases and as aborting in about one-third of the cases the course of the disease.

D. TYPHOID CARRIERS.

Every method should be utilized for the detection of typhoid carriers in armies, and further studies should be undertaken as a possible means of cure of these conditions, which have proved so refractory to the present time. We regard the present investigations which are being undertaken in several places on the carrier condition in rabbits as most promising in this direction.

THE PREPARATION OF THE PURE SODIUM PHOSPHITE AS AN ANTIDOTE FOR MERCURIC CHLORIDE POISONING*

By G. A. Linhart, Berkeley, Calif.

IN June, 1913, a preliminary paper was published by the writer,[1] dealing with the transformation of mercuric chloride to calomel in the body in cases of mercuric poisoning. Unfortunately, the work had to be discontinued owing to lack of money for the purchase of materials and animals. However, it is very gratifying to find that several investigators soon took up the problem, and, after extensive investigations, have conclusively substantiated my results, although none of these investigators have apparently seen my paper. I am quite sure that if they had they would have given it due recognition. A knowledge of its contents would have enabled them to interpret their results far more satisfactorily. Thus, Fantus[2] states that he is unable to explain why sodium bicarbonate alone has any antidotal value in cases of mercuric poisoning. The answer is that the metabolic changes taking place in the body are essentially oxidation-reduction processes. Hence, these numerous reducing substances react with the mercuric chloride at different but specific rates, which increase with decrease in concentration of acid; this decrease in the acid concentration is effected by the sodium bicarbonate. Another factor that has to be taken into account is the degree of complexity of the mercuric chloride, for the latter forms complex compounds[3] with other chlorides, and these complexes react exceedingly slowly[4] with reducing agents. Therefore, in order to obtain the best results, the condition of the system must be regulated accordingly. For example, every trace of acid must be previously neutralized if the reduction of the mercuric chloride to calomel by sodium phosphite is to be complete and instantaneous. To accomplish this without the introduction of an alkali, which is in itself poisonous, sodium salts of weak acids may be used. Sodium bicarbonate was found best for this purpose.

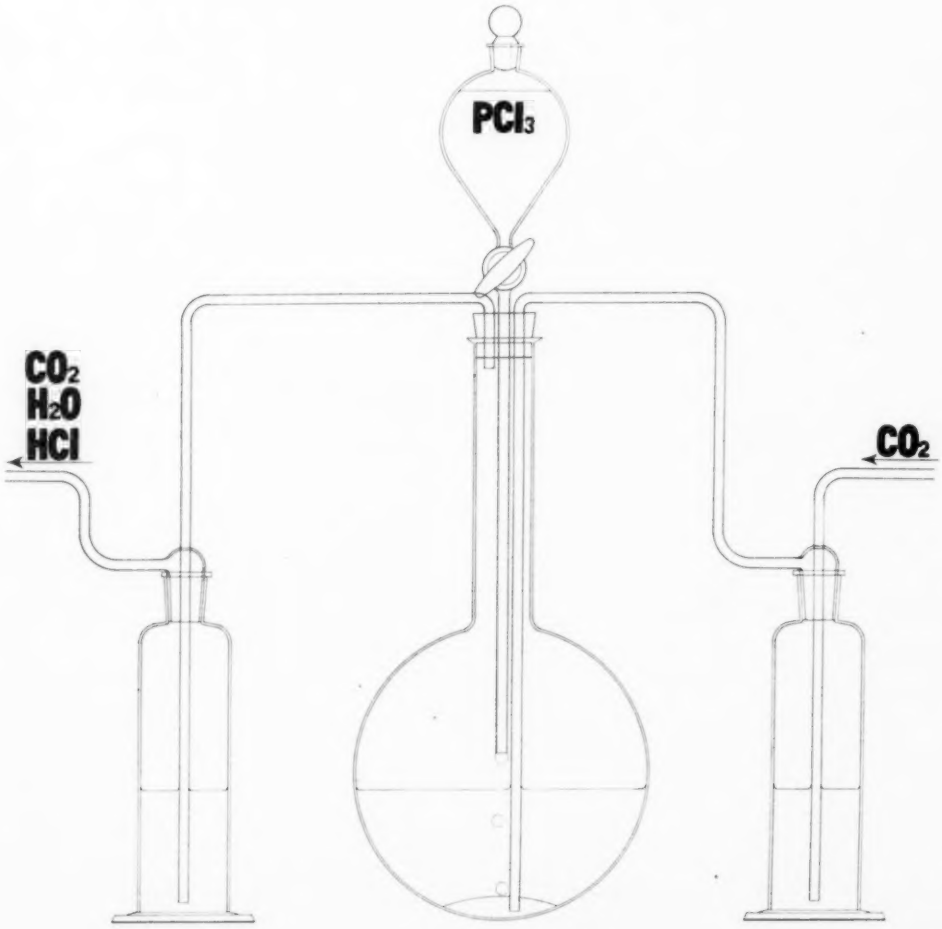
Theoretically a salt like sodium bicarbonate should be more effective in the neutralization of the acids in the system than sodium acetate because the reaction between sodium acetate and hydrochloric acid, formed in the reduction of mercuric chloride by reducing agents, is not complete, while the reaction between sodium bicarbonate and hydrochloric acid is instantaneous and quantitative, giving sodium chloride, carbon dioxide, and water. This is substantiated by experiment. The sodium chloride must, of course, be frequently removed together with the other products of the reaction by means of magnesium citrate or some similar substance, as the sodium chloride tends to retard the rate of the reduction of the mercuric chloride, owing to the formation of complex compounds previously mentioned.

Finally Fantus calls attention to the fact that a mixture of hydrogen peroxide and sodium hypophosphite is quite as efficient as sodium phosphite; but here again, he states that he is unable to explain "why hydrogen peroxide, an

*Contribution from the Department of Chemistry of the University of California.

oxidizing agent, should increase the efficiency of a reducing agent like hypophosphite." A theoretical discussion of this belongs to the realm of theoretical chemistry. It may, however, be of interest to point out that stoichiometrically the reaction between sodium hypophosphite and mercuric chloride in the presence of hydrogen peroxide is identical with the reaction between sodium phosphite and mercuric chloride. This is shown by means of the following equations:

1. $H_3PO_2 + H_2O_2 + 2HgCl_2 = H_3PO_4 + 2HCl + Hg_2Cl_2$
2. $H_3PO_2 + H_2O + 2HgCl_2 = H_3PO_4 + 2HCl + Hg_2Cl_2$



Moreover, hydrogen peroxide, as is well known, reacts with the blood, and is therefore very undesirable, especially for intravenous injections.

The publication of this paper at the present time is not merely to claim priority, for were it solely for this reason, it would not have been delayed until now. In fact, the two main reasons are, first, several physicians have requested me to publish the method of preparing the pure phosphorous acid as promised in my preliminary paper; and, second, I wish to suggest the possibility of administering rather large doses of mercuric compounds in infectious diseases, such as

syphilis, allowing the mercuric compound to remain in the system as long as possible and then removing the excess when necessary by means of sodium phosphite and sodium bicarbonate.

PREPARATION OF PURE PHOSPHOROUS ACID.

The method of preparing the acid is most conveniently described in connection with the figure.

The phosphorus trichloride is introduced into the separatory funnel, provided with a groove in the ground glass stopper for the admission of air, which permits the phosphorus trichloride to flow out into the flask via the stopcock. The phosphorus trichloride is allowed to flow into the water at such rate that there are never more than a few drops at the bottom of the flask. This is aided by passing a steady current of CO_2 gas, the function of which is also to prevent oxidation of the phosphorous acid by excluding the air.

The CO_2 entering the wash bottle on the right hand side is already purified, the function of this wash bottle being to supply moist CO_2 for the subsequent removal of the last traces of HCl. The wash bottle on the left hand side serves merely as a gauge to regulate the suction at the exit of the gases, (HCl, CO_2, and H_2O). If the rate of drawing off of the gases is too slow, fumes of HCl gas will appear at the cork stopper of the flask. When this happens, the suction must be increased sufficiently to just prevent the fuming, otherwise, a small amount of air will be drawn into the flask. The cork, as well as the holes through which the separatory funnel and the two tubes pass, is lined with platinum foil to prevent the action of the moist HCl gas on the cork stopper and the subsequent contamination of the solution below. The cork thus protected is more satisfactory than all-glass connections, as the whole apparatus is not so rigid and therefore less fragile. Moreover, the flask is made of "Pyrex" glass which is best for the purpose, but which can not be safely sealed onto any other glass, and there are as yet no "Pyrex" separatory funnels on the market.

After the desired amount of phosphorus trichloride has been allowed to react with the water in the flask,* (it is not necessary to cool the flask during the process) the wooden block upon which the flask rests (the flask is held in position by a clamp, not shown in the figure), is replaced by a water bath. The water is gradually warmed until its temperature is about the same as that of the melted paraffine bath by which the water bath is replaced. The paraffine bath is then gradually heated until its temperature is about 180° C. This temperature is maintained until the last traces of HCl are expelled. This is confirmed by replacing the wash bottle on the left hand side by another one containing a water solution of silver nitrate and nitric acid. The non-appearance of a white precipitate (AgCl) shows that the HCl has been completely removed. The paraffine bath is then removed and the flask is allowed to cool down to about 80° C., which is the melting point of phosphorous acid; during the cooling the current of CO_2 is continued. The liquid acid is then poured into any

*The amount of water to be used in the flask should be about 3 gram-molecular weight to one gram-molecular weight of phosphorus trichloride, or in the ratio of 54 grams of water to 137.5 grams of phosphorus trichloride, as is shown in the equation below. However, it is best to have the water in slight excess.

$$3H_2O + PCl_3 = 3HCl + H_3PO_3$$

desired form and allowed to solidify, preferably in the form of sticks. The sticks so obtained are put into bottles provided with ground glass stoppers.

The acid obtained by this process is chiefly meta-phosphorous acid or dehydrated acid, HPO_2, the rest being orthophosphorous acid or normal phosphorous acid, H_3PO_3. Both of these acids dissolve readily in cold water.

PREPARATION OF SODIUM PHOSPHITE.

In my preliminary paper attention is called to the fact that the commercial sodium phosphite is a mixture of NaH_2PO_3 and Na_2HPO_3, phosphate and other impurities, NaH_2PO_3 being the chief constituent. This can be shown even in a qualitative way, by suspending the commercial sodium phosphite in warm water and adding a solution of $NaHCO_3$. A considerable effervescence of CO_2 indicates the presence of NaH_2PO_3, while Na_2HPO_3 barely reacts with sodium bicarbonate, as the third or last hydrogen atom in the H_3PO_3 is not replaced to an appreciable extent by this method. It is, therefore, preferable to prepare the sodium phosphite solution from the pure solid stick-acid and pure $NaHCO_3$ whenever needed. Pure $NaHCO_3$ can be obtained from the Solvay Process Co., Syracuse, N. Y., through any reliable chemical concern. To test for the most common and undesirable impurity, Na_2CO_3, some of the sodium bicarbonate may be dissolved in cold water and a few drops of a solution of mercuric chloride added; a heavy reddish yellow precipitate indicates that considerable sodium carbonate is mixed with the sodium bicarbonate, while a mere opalescence or even a slight reddish brown precipitate shows that the sodium bicarbonate is fairly free from sodium carbonate.

Starting with the pure solid stick phosphorous acid and pure solid sodium bicarbonate, the following proportions by weight should be used for complete neutralization: $HPO_2 + 3NaHCO_3 = Na_2HPO_3 + NaHCO_3 + 2CO_2 + H_2O$, or in the proportion by weight of 1 to 4 of acid to bicarbonate, and the two dissolved in sufficient water to make about a 10 per cent solution.

It will be observed that this proportion of acid to sodium bicarbonate provides also for the subsequent neutralization of the last hydrogen atom after the Na_2HPO_3 has been oxidized to Na_2HPO_4 in the body, where the phosphite is administered as an antidote for mercuric chloride.

If the solution thus prepared is to be used for intravenous injections, it must, of course, be sterilized by filtration, and not by heating, as the sodium bicarbonate decomposes at about 47° C.

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References to the works of other investigators will be found in the article by Fantus, referred to above.

TRAUMATIC RUPTURE OF THE HEART: REPORT OF A CASE WITH UNINJURED CHEST WALL

By Ellis Kellert, M.D., Albany, N. Y.

SPONTANEOUS rupture of the heart is a not infrequent condition, and occurs more often than is commonly believed. Sudden death, in many instances ascribed to other causes, is found on postmortem examination to be due to coronary obstruction with subsequent infarction and rupture of a ventricle, or death may be caused by rupture of a fatty heart.

A few cases of cardiac rupture due to direct trauma applied to the chest have been described and in nearly all of these cases, fracture of the sternum or ribs with penetrating wounds of the heart were found. The case herein reported is of interest since it serves to illustrate that extensive trauma to the heart may occur with little or no injury to the thorax.

The accident took place near Ballston Spa. Mr. P. S., an Italian, aged 44 years, was engaged in digging in a sand bank. His fellow-workmen, a short distance removed, heard him cry out, and on turning about, found that the bank had caved in and the patient was surrounded up to the waist by a large quantity of sand. He was unconscious, but apparently alive. When dug out, he was dead. The above history is exceedingly meager, but no further information was obtainable.

At the autopsy, which was held eight days after death, the following conditions were found:

Bender Hygienic Laboratory No. A-15-26. The body, which has been embalmed, is that of a well built, muscular, white male adult. There is no evidence of injury to the skull. Over the upper anterior aspect of the chest, particularly on the left side, are five small abrasions measuring 0.5 to 2 cm. in diameter. Below the knees on both legs are several areas of abrasion, the largest of which, situated on the anterior surface of the right leg, measures 8x1 cm. There is no fracture of the bones of the extremities and no edema present.

Peritoneum.—The peritoneal cavity contains approximately one liter of bloody formalized fluid. The viscera and their position appear normal.

Thorax.—Examination of sternum and ribs reveals no fractures. Diaphragm: right, 6th interspace; left, 7th rib.

Pleural Cavities.—The right pleural cavity is entirely obliterated by firm fibrous adhesions. The surfaces in the upper portion are hemorrhagic and blood stained. The lung is voluminous, but crepitant. Cut section is grayish in color and dry, but somewhat firm in the posterior portion of the lower lobe, which is reddish on cross section. There is a slight bloody suffusion in the apical region. The left pleural cavity contains a large amount of fluid blood and blood clot—approximately one liter of clot and 800 c.c. of bloody fluid. Portions of clotted blood are firmly adherent to the chest wall and dome of the diaphragm. The left lung is compressed into the upper portion of the chest and is negative on examination.

Pericardial Cavity.—On opening the pericardium there is found a large amount of firm blood clot, surrounding the heart and adherent to the pericardial surfaces. The lower left portion of the pericardial sac presents a ragged opening 4 cm. in diameter, which is filled with firm friable blood clot and which communicates with the left pleural cavity.

Heart.—It weighs 370 grams. It is found to the right of the midsternal line and is twisted slightly from left to right. There is a large amount of firm blood clot adherent to the anterior and right lateral surfaces. Near the apex, on the right posterior surface, is a ragged linear laceration of the heart wall measuring 5 cm. in length. The margins are deeply blood stained and there is free communication with both ventricles, the tear extending across the interventricular septum. Just beneath the right auricle are two minute openings in the fat and myocardium. In the left ventricular wall beneath the

auricular appendage is a transverse laceration in the heart muscle measuring 2.5 cm. Near the apex, situated mainly in the epicardial fat, are two circular communicating openings (embalmer's needle?). The myocardium is dull red in color. The right side of the heart appears contracted. The wall measures 7 mm. in thickness, but appears very thin near the laceration above described. Within the cavity there is found a small amount of friable blood clot. The papillary muscles are greatly lacerated, the surfaces rough and blood stained. The portion attached to the chordæ tendinæ is found free in the auricle. The tricuspid valve appears negative. The endocardium of the right auricle above the valve is markedly lacerated. The left ventricular wall measures 1.5 cm. to 2 cm. in thickness. In the left ventricle there is a very small amount of friable blood clot present. The papillary muscles have been torn from their attachments to the cardiac wall and their surfaces are very irregular, blood stained, and appear lacerated. The interventricular septum near the apex is greatly lacerated. The valve leaflets are intact. The aorta at its origin is separated through one-half the circumference, the margins being sharp, as though incised.

Fig. 1.—Heart, showing transverse rupture near apex.

Gastrointestinal Tract.—No injury or hemorrhage is found.

Liver and Pancreas.—Appear normal.

Spleen.—It is enlarged and somewhat soft. The capsule is everywhere adherent to the peritoneal surfaces. Cut section is bright red in color. Surface scrapings are moderate. At the hilus is found a small spherical mass of splenic tissue.

Kidneys.—They are normal in size and weight, and are surrounded by a moderate amount of perinephritic fat. The capsule strips readily, exposing a markedly injected surface. Cut section is reddish-brown in color and the papillæ are congested. Bloody fluid escapes. In the outer portion of the cortex of the left kidney is a minute opening about which is fragmented kidney substance and from which blood escapes.

Adrenal Glands.—They are normal.

Bladder.—It is normal.

Histology.—

Heart.—Slight amount of fatty infiltration of the right ventricular wall. Increased amount of pigment about the nuclei, which vary greatly in size and have blunt ends. An

occasional area of fibrosis is present and a rare focal accumulation of lymphocytes, endothelial cells and polynuclear leucocytes. Vacuolation is present in the muscle fibers.

Lung.—The vessels are distended and filled with blood. The capillaries in the alveolar walls are also dilated and filled with blood. Many red blood cells are found free in the alveoli.

Spleen.—The Malpighian corpuscles are small. There is a marked endothelial hyperplasia, and numerous eosinophiles are present.

Kidney.—Vessels prominent and filled with blood. Tubules negative. Glomerular tufts voluminous, and many are distended with blood. A small area in the capsule and adjacent cortex is suffused with blood.

Aorta.—Slight sclerosis and a few small areas of calcification in the media.

Head.—The brain was not examined.

ANATOMICAL DIAGNOSIS.—Multiple ruptures of the heart; hemopericardium; rupture of the pericardium; hemorrhagic effusion of the left pleural cavity; subpleural hemorrhage; chronic pleuritis; chronic interstitial myocarditis; acute congestion of lungs and kidneys; small rupture of the left kidney; chronic peritonitis; chronic splenitis and perisplenitis; accessory spleen; superficial abrasions.

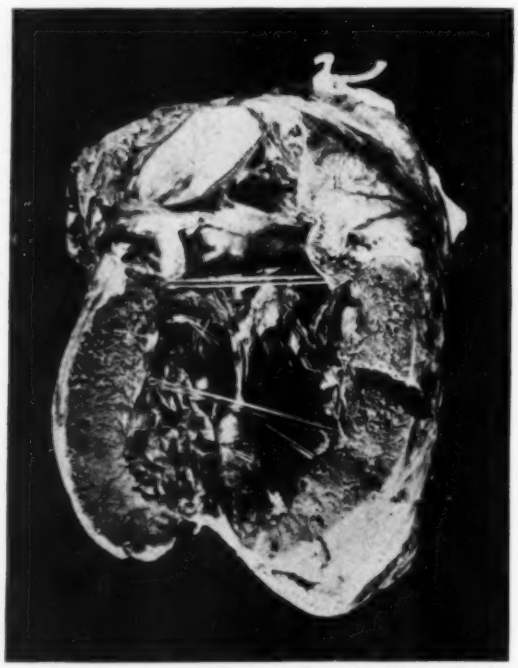

Fig. 2.—Heart, left ventricle. Note torn papillary muscle.

In the many cases of traumatic heart rupture already reported, severe injury to the chest wall has been the rule. A few exceptions are worthy of brief mention.

Dufour[1] reports the case of a girl thirteen years of age who underwent severe compression by a man and in addition presented stab wounds about the neck. A rupture of the right auricle was found, but no wound of the chest wall or pericardium.

McOscar and Voelcker[2] describe the case of a man who was run over by an empty wagon and died eight days later. At the necropsy there was found a transverse rupture of the ventricular septum one inch in length. No fractures of the ribs or sternum, and no lacerations of the abdominal viscera were present.

O'Neil[3] gives the autopsy findings in a boy aged nine years who was knocked down and jumped upon by other boys. He walked home, but died at the end of eight days. At the necropsy there was found a hemopericardium and a small rupture at the auriculoventricular junction of the left heart. All other organs were negative and since no mention is made of wounded chest or fractured ribs, it is assumed that none were present.

Kugel[4] described the case of a man forty-four years of age working in a cotton-spinning mill. He was killed by one of the heavy balls falling upon his chest and died forty-two hours later. At the autopsy there was found a hemopericardium and a sharp tear in the right ventricle. The heart was enlarged and fatty masses were present on the surface of both ventricles. There were no fractures or changes in the other organs.

Copeland[5] cites a case of ruptured aorta, occurring under circumstances simi-

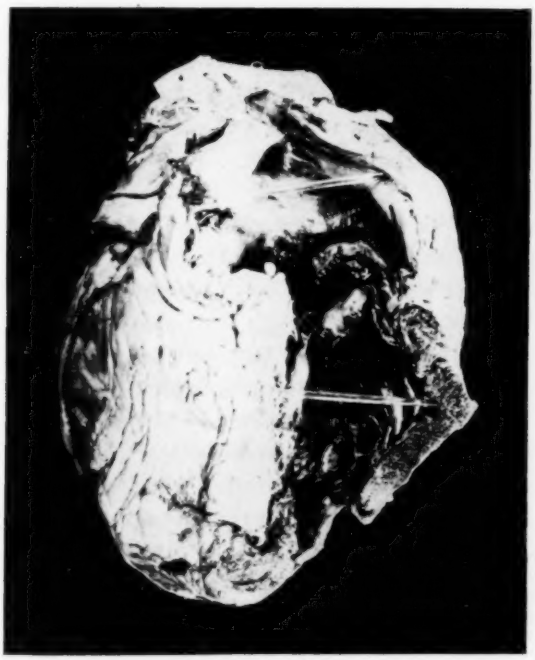

Fig. 3.—Heart, right ventricle, showing ruptured papillary muscle.

lar to the one here reported. His patient, a laborer aged forty years, was struck by falling earth but only the legs were covered. There was found a rupture of the descending aorta into the left pleural cavity which contained thirty-eight ounces of blood. He suggests a force acting in contrecoup.

Robertson[6] reports a man of forty-nine falling from a railway carriage and striking the ground with his left shoulder. He died in forty-five minutes. At the autopsy the pericardium was found intact, but a rent one and one-fourth inches long existed in front of the left auricle. There was no wound of the chest. Of course one must in this case consider the possibility of the rupture having occurred just prior to the fall although the situation in the auricle is very unusual for spontaneous rupture of the heart.

Gibbons[7] relates the following history. A coolie was struck over the chest as well as elsewhere with a bamboo stick. He fell to the ground and vomited, dying three hours later. A livid scratch over the right side of the chest was found but no penetrating wound. The heart showed a rupture at the apex, communicating with the right ventricle. The musculature at the point of rupture appeared very thin but no mention of aneurism is made.

The case of a man kicked on the chest by a horse is recorded by Hutchinson.[8] A hematoma precordia was produced, but the skin remained unbroken. The patient died fourteen hours later. There was a rupture at the apex of the right ventricle and the pericardium presented a tear anteriorly.

Groom[9] reports a lad sixteen years of age, was caught between the shaft of a pony cart and a wooden railing. Death occurred a month later and there was found a rupture in the posterior portion of the left ventricular wall one inch in length. A cardiac aneurism had developed at this point which later burst.

Peacock[10] relates the case of an athlete aged 25, who after a wrestling match became intoxicated and in a quarrel received a blow in the epigastrium from a clenched fist. He became unconscious and died in forty minutes. The autopsy disclosed a rupture of the right ventricle three and one-half inches in length, extending from the base to the apex. The valves were normal and no atheroma was present.

There are two possibilities in explanation of the lesion in the present instance. First, that the weight of the falling earth, which being soft and adaptable, caused equal pressure over the chest resulting in great compression and bursting of the heart, very much as though a rubber bag distended with fluid were compressed at its middle. To obtain such an effect without fracture of the sternum or ribs seems very unlikely. The second and more probable explanation is that of hydraulic pressure. The large quantity of sandy soil exerted such great pressure over the lower half of the body as to drive most of the blood out of the vessels. This produced sudden over-distention of the heart, which was probably dilated as a result of physical exertion, with consequent rupture at several points. That the force was a great one is indicated by the ruptured pericardium and hemorrhages in the lung. The pathologic changes in the heart, though not very marked, undoubtedly contributed to the severity of the injury.

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ACUTE TUBERCULOUS PARIETAL ENDOCARDITIS*

By John R. Stark, M.D., Cincinnati, Ohio.

CARDIAC tuberculosis is not particularly uncommon. It appears in the form of myocardial, epicardial, valvular and mural infections. The myocardial disease may be of hematogenic origin when it is limited to that tissue or it may be the result of extension from epicardium or endocardium. Usually it is of epicardial origin. Epicardial tuberculosis is more frequent, so frequent, indeed, as to need no comment. Endocardial tuberculous lesions in the pure form are by far the most infrequent tuberculous cardiac lesion, and have been the subject of much study. In the less pure forms of endocardial involvement the evidence is that the bacilli reach the endocardium by way of the myocardial and subendocardial blood vessels, and therefore, as a rule, the myocardium is also involved. In the pure forms the infection must occur from bacilli present in the main blood stream which are able to become attached to the endothelial cells of the endocardium.

If so many tuberculous lesions are hematogenic in origin it must be true that tuberculous septicemia is not particularly uncommon; and if that be true, then the opportunities for endocardial infection must be numerous. It is perhaps the rapidity of the blood in the large open spaces of the heart that prevents lodgment of the bacteria, and it is the same factor, plus perhaps the presence of but small numbers of bacilli in the blood, that accounts for the rarity of pure parietal tuberculous endocarditis. In Marshall's[1] series of cases the tuberculous process seems to have appeared invariably beneath the endocardium, irrespective of the localization in the valves or in the mural endocardium.

Since Corvisart[2] reported his case of tuberculous pericarditis, and suggested the occurrence of tuberculous endocarditis, considerable study has attached to these lesions. The major amount of these various contributions has been reviewed by Norris[3] who credits Corvisart with an account of mitral valvular tuberculosis. But so far as I can discover, Corvisart's case was one of pulmonary tuberculosis complicated with vegetative mitral endocarditis, for, to use his own words (in translation), "the mitral valves and semilunar of the aorta were covered with vegetations exactly like venereal warts observed upon the glans and prepuce of persons affected with syphilis" (pages 180-181). But Corvisart does describe a case of tuberculous pericarditis, and he does it very definitely.

In the entire published series of cases of cardiac tuberculosis there appear, so far as I can discover, but two in which the lesion was definitely in the endocardium,—those of Schultze[4] and Rheinhard.[5] Only in the report of Rheinhard, however, are there definite pictorial descriptions of the lesions. Benda,[6] in discussing subendocardial or myocardial tubercles and in differentiating between true endocardial lesions, laid down the rule that the structure of the internal elastic lamella, would serve as the best criterion. If this were damaged, the evidence led in the direction of a primary subendocardial lesion.

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While I do not agree completely with the rule of Benda, the case which is to be reported conforms to it and, therefore, appears to be the third authentic case of primary acute parietal or mural tuberculous endocarditis to be recorded.

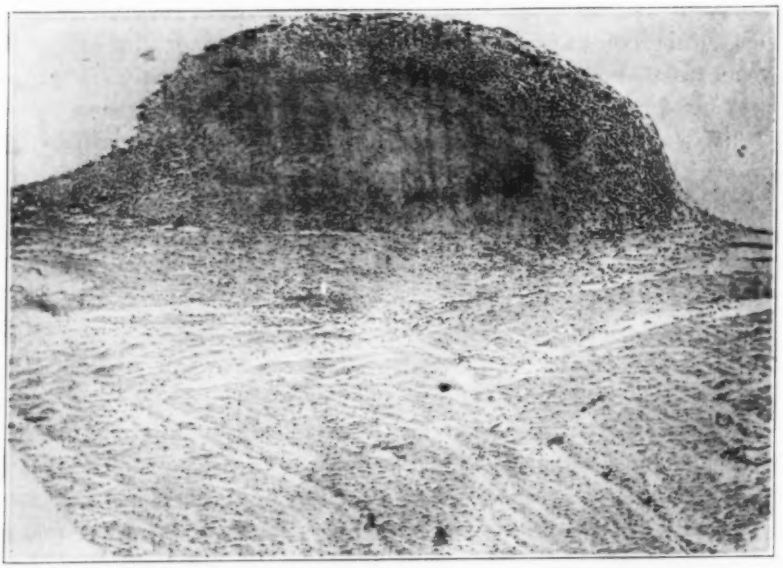

Fig. 1.—The entire tuberculous nodule with caseating center and intact endothelium, except at one point, situated within the endocardium. It shows the typical base consisting of epithelioid and round cells with fairly numerous typical giant cells. The endothelial lesion is probably an artifact.

Fig. 2.—A resorcin-fuchsin specimen to show that the caseating mass is entirely above the elastica interna. There is very slight evidence of subendocardial reaction visible at only one point in the myocardium.

CLINICAL NOTES.

The patient, J. M., Hospital No. A-7524, was admitted into the Cincinnati General Hospital on the Orthopedic Service, on November 11, 1916, and died March 23, 1917.

Unfortunately in the hospital records there was no history of the past illnesses or present condition of the patient who was a negro porter aged 32 years. The record consisted of daily notes as to the clinical condition of the patient, operative procedures, x-ray reports, and urinalyses. The important features gleaned from these meager notes are that an x-ray examination taken a few days after admission on November 14, "showed gross destruction of the body of the first lumbar vertebra and also some changes in the body of the twelfth dorsal." On this same day the patient was operated and two large abscess cavities located somewhere along the spine were opened and drained. He gradually improved from this time on and January 11, 1917, a cast was applied and he was allowed up in a chair for a short time. A urinalysis on January 31 showed a cloudy, amber, alkaline urine with a specific gravity of 1012, albumen positive, and microscopically many pus cells, hyaline and granular casts but no blood. The next clinical note recorded about two months later, the day of death, states: "The patient has been gradually growing weaker. Tuberculous meningitis set in 3/18/17. The patient became violent, then went into coma 3/22/17, and died 3/23/17 at 9:10 A.M."

Clinical Diagnosis.—Dorsal and lumbar Potts; tuberculous meningitis.

With this we must be content.

AUTOPSY PROTOCOL.

The body was that of a greatly emaciated colored man of about 35 years of age. The body was still warm and postmortem rigidity had not yet set in. The muscles of the right arm were more atrophic than those of the left. There was no noticeable difference in the muscles of the legs. On the back, over the 11th and 12th thoracic and first two lumbar vertebræ, there was a superficial abrasion, and in the region of the 12th vertebra there was a gibbus. The gibbus, however, was also made up of the 11th and 12th and the 1st and 2nd vertebræ. Below over the sacrum, there was a strip of adhesive tape covering a small sinus from which there oozed a quantity of thick yellowish pus. To the left of the spine, beneath the 12th rib there was a larger sinus from which a similar purulent material poured out. The pupils were equal and slightly dilated. The teeth were in fair condition and there was only a moderate pyorrhea. There was marked anemia of all the mucous membranes. At the base of the neck there was a symmetrical swelling as from a goitrous enlargement. There was no peripheral glandular enlargement except for a few small pea-sized inguinal glands. The musculature over the chest and abdomen was greatly diminished; there was no subcutaneous fat.

When the sternum was removed, the lungs partially collapsed. There were no pleural adhesions nor any fluid in the pleural cavities. There was about 25 c.c. of clear straw-colored fluid in the pericardial cavity. The lungs upon removal, crepitated throughout. The apices were not scarred and there were not even interlobar adhesions. On section, the lungs were perfectly healthy throughout.

The heart was slightly enlarged and extremely pale. The left side was rather firmly contracted while the entire right side was very flabby and dilated. There was no valvular abnormality throughout. The aorta was perfectly clean. Just beneath the endocardium of the left ventricle about 3 cm. from the apex on top of a columnus carnea there was a somewhat whitish, slightly firm, raised nodule about 2 mm. in diameter which on section appeared homogeneous and was perhaps a tubercle. The myocardium itself was pale and presented a few areas of fibrous bands. These were particularly marked in the tips of the papillary muscles.

Upon opening the abdomen there was no excess of fluid. The peritoneum was shiny throughout and the omentum lay curled up over the transverse colon. The intestines were thin and shrunken, the appendix was *in situ* and free from adhesions. Upon removal, the entire gastrointestinal tract was healthy except for one small ulcerating tuberculous mass about 1 cm. in size, in the ascending colon just above the cecum.

The spleen was enlarged. The capsule was smooth and shiny, but beneath it there could be seen numerous large and small whitish areas. On section, the spleen showed numerous miliary and conglomerate tubercles, the largest not over 3 mm. in size. The parenchyma of this organ, except for this, showed no change. The liver was pale and beneath its capsule could also be seen a few miliary tubercles. The organ cut with increased difficulty and throughout it were seen occasional miliary tubercles. The organ

itself was extremely pale and cloudy, but its consistency was generally increased, yet showed no gross evidence of fibrous tissue. The gall bladder was free from adhesions and contained a dark clear bile. The right kidney was enlarged, and of a pale red color. It cut with increased resistance and showed numerous conglomerate tubercles, none measur-

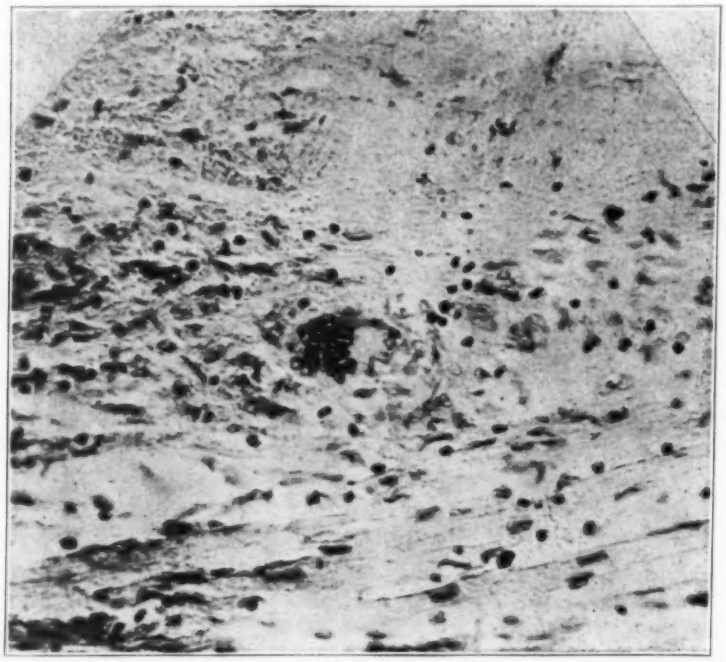

Fig. 3.—A larger magnification of the base showing two typical giant cells with numerous round and epithelioid cells.

Fig. 4.—A typical acid-fast bacillus of the slightly curved type lying in the richly cellular area. These bacilli were quite numerous but were seldom found lying parallel with the plane of section, hence the hazy, indistinct outline in the photomicrograph. They were usually curved and irregular and possibly were of the branching type, as described by Woolley[7] in "acute tuberculous endaortitis."

ing more than 3 mm. in size. The cortex was thickened, not well marked off from the medulla, and had a pale pinkish color. There was no evidence of Malpighian corpuscles. The capsule stripped easily, leaving a smooth surface. The stellate veins were not injected. The right ureter was distended to about the size of a pencil to its entrance in the bladder. The pelvis was apparently healthy. The left kidney was tremendously enlarged. It was adherent to the psoas muscle behind and was removed with great difficulty. In removing it the kidney substance was torn and a considerable amount of watery yellowish pus was expressed from an opening on the posterior surface of the organ which extended into the psoas muscle. The kidney itself showed a very thin cortex in which were numerous miliary and conglomerate tubercles. The entire medulla and pelvis were replaced by a large tuberculous abscess cavity which was somewhat cauliflower in shape and extended throughout the kidney. The left ureter was obliterated by a firm white glistening columnar mass of tuberculous tissue about 1½ cm. in diameter, which extended from the pelvis to the bladder. No lumen was discernible. The bladder was distended to about two inches above the pubis, and was filled with a very cloudy turbid amber-

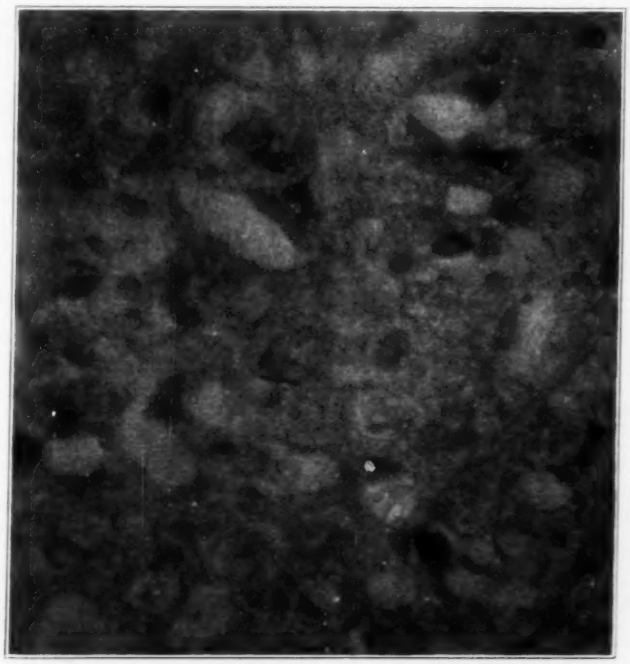

Fig. 5.—A straight beaded acid-fast bacillus in the endocardial tubercle.

colored urine. Many flocculent white masses floating in the urine contained calcium salts. The mucosa was of a pale white color and was covered by these flocculent masses. The bladder wall showed numerous miliary tubercles, but no ulceration. At the opening of the prostatic urethra, the entire mucosa was ulcerated and covered with tuberculous granulations. The prostate was small and apparently healthy. After removal of all the abdominal viscera, it was seen that the body of the 12th dorsal vertebra was eroded and softened on the left side and in the region of the pedicle the bone was completely eroded and destroyed so that the finger could be introduced into the spinal canal.

Permission was not obtained to open the calvarium or explore the spinal canal further. The lymph nodes along the course of the abdominal aorta, more particularly upon the left side, and extending down into the pelvis along the iliac vessels, were greatly enlarged, firm, and, upon section, appeared to be completely replaced by tuberculous material. The thyroid was enlarged, the right lobe slightly more so than the left. It cut with rather increased resistance and was extremely pale. In the upper pole of the right lobe there was a small, white, fine stellate area possibly tuberculous, but appearing more like a mass of fibrous tissue. There were no cysts.

Anatomic Diagnosis.—Chronic tuberculous spondylitis; psoas abscess; chronic tuberculous nephritis; chronic tuberculosis of the retroperitoneal glands; metastatic tubercles of the liver, spleen, right kidney, adrenals and possibly the myocardium; tuberculous colitis; chronic tuberculous cystitis and ureteritis; amyloidosis of the liver and kidney; cardiac dilatation; myocardial fibrosis; hypertrophied thyroid.

Realizing at the time of autopsy the great infrequency of endocardial tuberculosis, and not appreciating in the gross specimen that the tubercle was entirely in the endocardium, the anatomical diagnosis and necropsy report were first conjectured, but later proved by microscopical sections.

Although this case, at first glance, might be considered one of generalized miliary tuberculosis, yet it presents many interesting features. The entire absence of any pulmonary or peritoneal involvement is truly unusual. The kidney lesion was evidently one of extension from the tuberculous spondylitis. Involvement of spleen and liver were minimal.

The accepted theory of acute generalized miliary tuberculosis is that a tuberculous focus adjoining some blood vessel erodes the vessel wall and the bacteria are disseminated throughout the body. In this case we have another source for the scattering of the bacilli. Had the patient lived longer an ulcerated area might have been met with together with a greater involvement of the abdominal organs. However, since tubercle bacilli are accredited with the power of traversing intact intestinal mucous membrane, it seems entirely possible that the existing foci might have been due, in part at least, to the passage of the bacteria from the caseating mass through the intact endothelium.

There are perhaps forty cases of tuberculous endocarditis described, and only three of true tuberculous parietal endocarditis. This same relation between vegetative and mural endocarditis of other bacterial origin is met with. This fact is very suggestive of the infrequency of implantation endocarditis as compared with the more accepted embolic theory.

CONCLUSIONS.

1. This is the third recorded case of tuberculosis of the parietal endocardium.

2. Here is definite evidence of the implantation theory of endocarditis, however infrequent.

In conclusion, I wish to thank most sincerely Dr. P. G. Woolley, Director of the Pathologic Institute of the Cincinnati General Hospital, for his kindness and encouragement in the above, and Mr. O. Haude, for his energy and skill in procuring these most excellent sections and photomicrographs.

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LABORATORY METHODS

DESCRIPTION OF AND PLANS FOR THE INSTALLATION OF A BLAST AND VACUUM PUMP*

By Wm. H. Welker, Chicago, Ill.

INTRODUCTION.

THE form of installation applied to the blast and vacuum apparatus in this laboratory has frequently been the subject of favorable comment on the part of visitors. A number of requests have been received for scale drawings and a general description of the installation. It seemed probable, therefore, that the publication of a description accompanied by working drawings, might be of benefit to the workers in laboratories not supplied with blast and suction from a central plant.

The machine used is the Crowell Rotary Blast and Vacuum Pump, catalogued by most of the apparatus supply houses. The installation described, is the result of six years of experimentation with this form of machine. The advantages of this type are as follows: Its original cost is comparatively low; the operating and maintenance costs are low; it is noiseless in operation; it is possible to secure pressure up to 40 pounds per square inch and vacuum down to 29 inches of mercury; and blast and suction within certain limits are obtainable simultaneously.

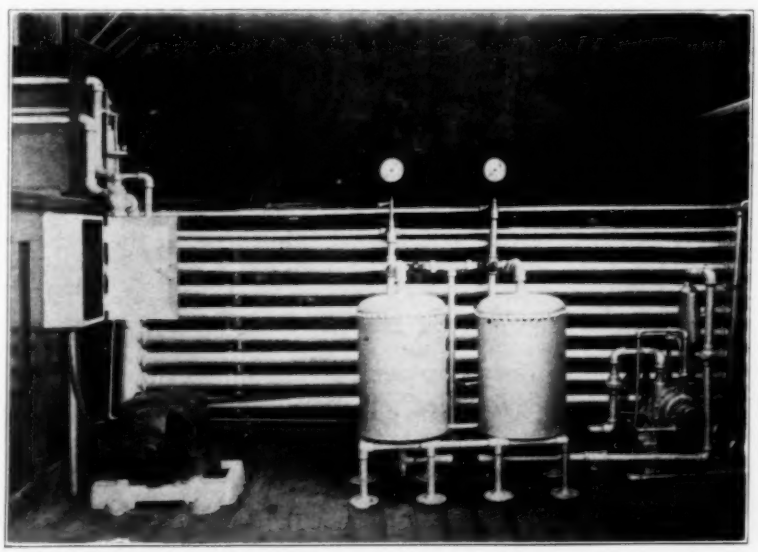

Fig. 1.—Photograph of the installation in the Laboratory of Physiological Chemistry, College of Medicine, University of Illinois.

*From the Laboratory of Physiological Chemistry, College of Medicine, University of Illinois.

USES.

In this laboratory, the apparatus is used for running blast lamps, stirring solutions, handling liquids, drying by air current, artificial respiration (with interruptor interposed,) vacuum distillation, aeration, and suction filtration. The liquids that are handled by compressed air include a strong solution of alkali for the Kjeldahl distillation work. The arrangement consists of a delivery tube which runs to the bottom of the bottle serving as container for the solution. A "T" tube serves to connect the pressure line with the container, the third opening being closed with the finger when it is desired to transfer liquid from the container to another vessel. Special mention is made of this point because con-

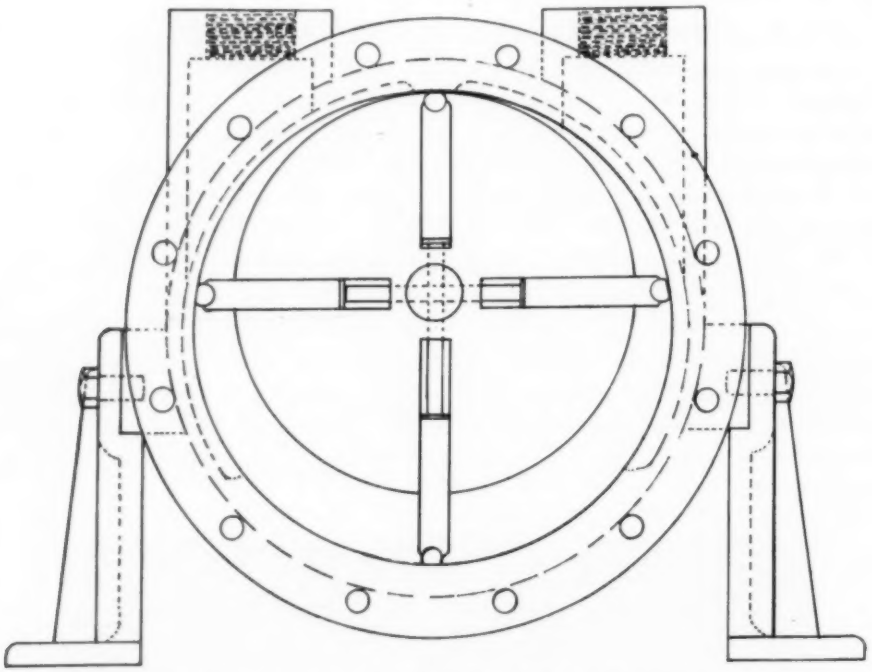

Fig. 2.—The plan of interior construction of the Crowell Rotary Blast and Vacuum Pump. (Courtesy of The Crowell Mfg. Co.)

siderable effort has been given by laboratory workers, to the construction of special apparatus for the handling of this solution.

INSTALLATION.

One of the first difficulties encountered in the installation of this machine originated in the fact that the smaller alternating current motors obtainable on the market are built to give a speed of 1800 R.P.M. The smallest pulley that manufacturers recommend for this motor is 2½ inches in diameter. This necessitates a 9 inch pulley on the machine to give it the operating speed suggested by its manufacturer. The 9 inch pulley dips below the level of the frame of the machine and an idler had to be placed under the belt to prevent it from scraping on the latter. This idler caused considerable trouble and was noisy. The diffi-

culty was finally overcome by placing hardwood blocks between the machine and its frame, thus raising the bottom of the pulley sufficiently for the belt to clear the frame.

Brass lever stopcocks are used for regulating the pressure and vacuum in the tanks, instead of the adjustable spring valves furnished by the manufacturers.

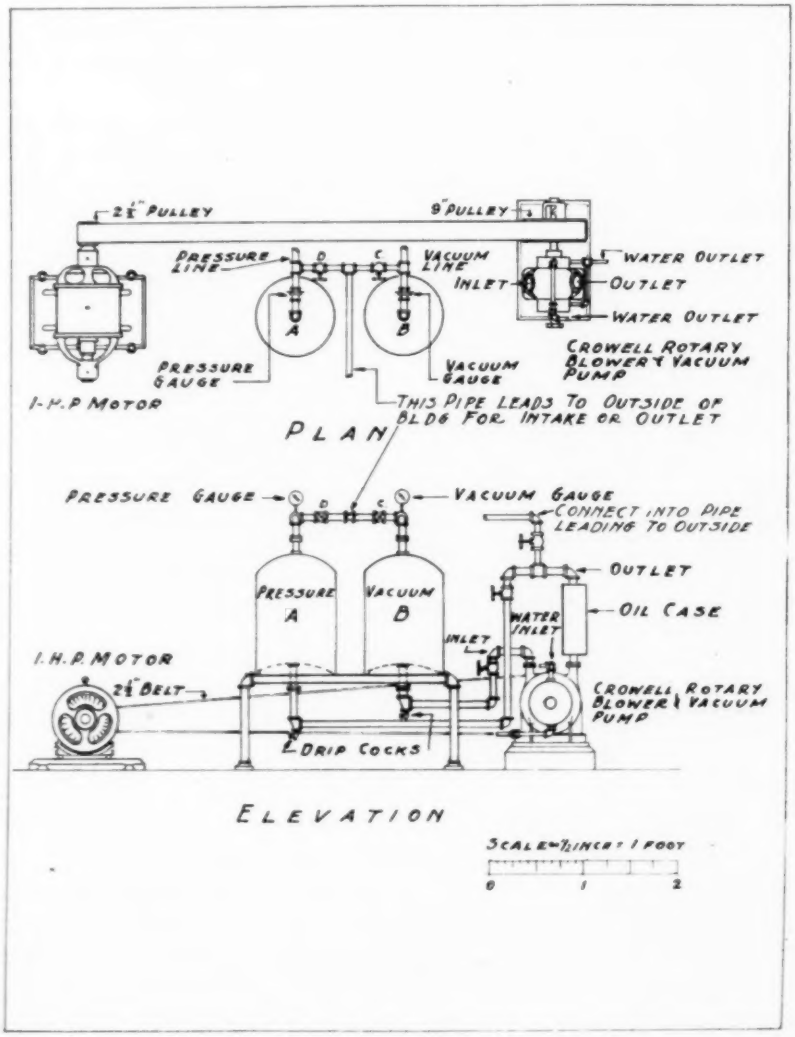

Fig. 3.

Adjustments can be more easily and accurately made with the lever stopcock than with the spring valve. Wherever gate valves appear in the plan, brass lever stopcocks are actually used in the installation. The escape of excess compressed air through either spring valve or stopcock is a noisy operation. The same is true of the operation of either of these valves on the vacuum tank. The noise was completely eliminated by connecting with the blast outlet "D" and vacuum intake "C," a common pipe leading to the outside of the building.

By closing the respective stopcock on the line from the machine to the tank, compressed air or vacuum may be stored so that it can be used after the pump has been stopped. This method is especially well adapted for the vacuum filtration of difficultly filterable solutions.

In the vacuum distillation of ether, alcohol, and liquids of similar character, explosive mixtures will be carried into the pressure tank. To prevent this, a crossover with stopcock has been placed between the line from the machine to the pressure tank and the line to the outside of the building. By opening this stop-

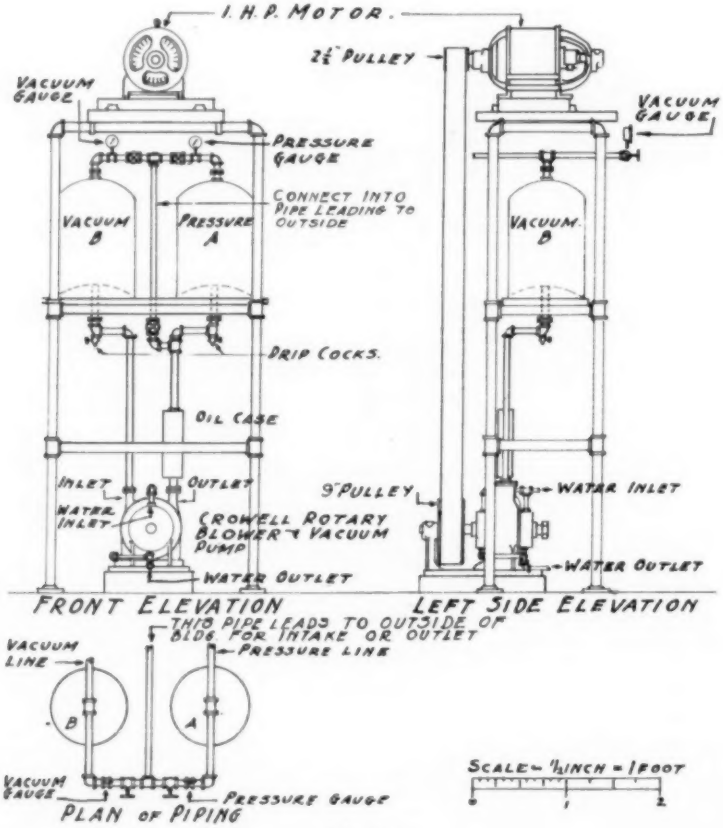

Fig. 4.

cock and closing the stopcock in the line leading to the tank and also the stopcock "D," the mixture of explosive gases is conducted directly to the outside of the building.

I am indebted to Mr. Tracy, formerly of this staff, for assistance in some of the experimental work on the installation. I am indebted also to Professor White, supervising architect of the University, for the preparation of the scale drawings, and for the suggestion of the vertical form of installation. Where floor space is limited, this plan of installation would be preferable to the horizontal one.

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EDITORIALS

Dried Tetanus Antitoxin

SOME months ago the Committee on Medicine and Hygiene of the National Research Council took up this subject, having learned that such a preparation was being used in the German army. It turns out that Robertson, of the University of Minnesota, was at work with Aschoff in Freiberg, Germany, on the preparation of dried tetanus antitoxin during the first year of the war. Robertson writes as follows:

"I may state that we felt that the results of our experiments would justify us in trying to produce a first-aid method of administering tetanus antitoxin by drying it on pieces of gauze or cotton and carrying it in this dried condition in the first-aid package. It was found that if these dried pads were placed on wounds they gave protection to animals which had received from two to five times the minimum lethal dose of tetanus toxin. During the past two years I have been working in my spare time on the dose of antitoxin necessary for prophylactic purposes. While my experimentations are not finished, they point to the possibility of considerable reduction in dosage with full and adequate amount of defense provided. The short time that the antitoxin immunization

persists renders, in a great many cases, a second dose necessary in any event, and the smaller doses seem to be fully as sufficient as larger ones."

It is not supposed that the dried antitoxin will do away with the necessity of antitoxin injections. A bit of the cotton containing the dried antitoxin is moistened with a sterile water or salt solution and applied to the wound in the first-aid dressing. Then, as soon as possible, the antitoxin injection is given.

—*V. C. V.*

Blood Alkalinity and Cancer

ANY procedure which will make possible the more certain diagnosis of cancer, is valuable. There are times when a cancer is suspected in a patient at a period during which operative procedures might be carried out with success, and yet in such patients there is a reasonable doubt which leads to a diagnosis of some less serious condition which is not to be treated radically.

Menten[1] in a study of blood alkalinity (i.e., the hydrogen-ion concentration) has reached the general conclusion that while the alkalinity of the blood serum may be increased or diminished in various diseases, yet almost without exception the cases of malignant disease, that is, cases of cancer of the skin and internal organs, and of sarcoma, show a characteristic change in the reaction of the blood serum. This change consists in a marked increase in the alkalinity of the serum. In contrast to these findings are the results obtained in cases of tuberculosis, rheumatism, pemphigus, nephritis and heart lesions accompanied by dyspnea in all of which the acidity of the serum is increased. The increase in alkalinity of the serum in malignancy is so constant and of so marked a character when the growth occurs in the internal organs that it is believed that it may furnish an additional diagnostic aid of value, particularly, in early stages.

Menten used the gas chain method in determining the hydrogen-ion concentration of the blood, a method which is not usable by the ordinary laboratory man or by the clinician who makes his own determinations, but it is entirely possible that one of the simpler methods in vogue may be of rapid clinical value.

It is interesting to speculate upon the relation of the alkalinity to malignant growth. Is is cause or effect? Menten mentions a case in which, after the administration of sodium bicarbonate, the rate of growth of a cancer was hastened.

High alkalinity is not a certain indication of cancer, but its presence in a suspected case is an added reason for a positive diagnosis. The method therefore is like practically all other laboratory tests, merely an aid, perhaps a very valuable one, to the careful clinician. To the careless one it is apt to be a hindrance, or to be misleading. Albumin and casts do not necessarily mean nephritis. These appear in other conditions,—but their presence, under certain conditions, is highly suggestive.

—*P. G. W.*

[1]Menten: Jour. Cancer Research, 1917, ii, 179.